Roadmap: proton therapy physics and biology

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Roadmap: Proton Therapy Physics and Biology

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Abstract

The treatment of cancer with proton radiation therapy was first suggested in 1946 followed by the first treatments in the 1950s. As of 2020, almost 200,000 patients have been treated with proton beams worldwide and the number of operating proton therapy facilities will soon reach one hundred. Proton therapy has long moved from research institutions into hospital-based facilities that are increasingly being utilized with workflows similar to conventional radiation therapy.

While proton therapy has become mainstream and has established itself as a treatment option for many cancers, it is still an area of active research for various reasons: the advanced dose shaping capabilities of proton therapy cause susceptibility to uncertainties, the high degrees of freedom in dose delivery offer room for further improvements, the limited experience and understanding of optimizing pencil beam scanning, and the biological effects differ from photon radiation. In addition to these challenges and opportunities currently being investigated, there is an economic aspect because proton therapy treatments are, on average, still more expensive compared to conventional photon based treatment options.

This roadmap highlights the current state and future direction in proton therapy categorized into four different themes, "improving efficiency", "improving planning and delivery", "improving imaging", and "improving patient selection".

Introduction to the Proton Therapy Roadmap

Harald Paganetti and Tony Lomax

The dosimetric advantages of proton radiation therapy compared to 'conventional' photon radiation therapy were first outlined by Wilson in 1946 (Wilson, 1946). He presented the idea of utilizing the finite range of proton beams for treating targets deep within healthy tissue, and was thus the first to describe the potential of proton beams for medical use. Wilson's suggestion to use protons was based on the well-known physics of protons as they slow down while penetrating tissue, causing the Bragg peak and completely stopping in the patient.

While the advantage of protons was seen from a physics (dosimetric) perspective, any new radiation treatment technology has to find acceptance amongst clinicians by demonstrating that the improved dose distribution leads to a more favorable treatment outcome (Suit et al., 1975). When proton therapy was first introduced it was of interest mainly because it showed dose conformity far superior to any type of conventional photon radiation therapy at the time (Suit and Goitein, 1974; Suit et al., 1977). The difference in target dose conformity between protons and photons, at least at high doses, has however largely disappeared since the early days of proton therapy (at least for regularly shaped targets), mainly due to the development of intensity-modulated photon therapy and its extension to rotational therapies. Today, it is quite feasible to reach high-dose conformity to the target with photons that is comparable to the one achievable with protons, albeit at the expense of using a larger number of beams. However, the integral dose (the total energy deposited in the patient) is always lower with proton beams (by a factor of at least 2-3 (Lomax et al., 1999)), i.e. proton treatments avoid the 'dose bath' to healthy tissue that patients are exposed to with photon techniques. Indeed, there is a limit to further improving and shaping photon generated dose distributions because the total energy deposited in the patient, and thus to critical structures, cannot be reduced but only distributed differently. Proton radiation therapy, on the other hand, can still achieve further improvements through the use of scanning-beam technology and intensity-modulated proton therapy.

Proton therapy is already an established treatment option for many tumor types and sites. For instance, it is well recognized that protons are extremely valuable to treat tumors close to critical structures, e.g.,

for head-and-neck treatments (Chan and Liebsch, 2008). In the pediatric patient population however, the impact of the decreased total absorbed energy in the patient with protons seems most significant. The overall quality-of-life and reduction of secondary effects is particularly important and the reduction in overall normal tissue dose has proven to be relevant for short and long term toxicities (Indelicato *et al.* 2019, Xiang et al. 2020). One prime example is the treatment of medulloblastoma, where treatment with photon radiation therapy invariably causes significant dose to the heart, lung and abdominal tissues, as well as organs at risk in the cranium, something that can largely be avoided using protons (Kamran *et al*. 2018). The reduced integral dose with protons is also beneficial when radiation is combined concurrently with chemotherapy (Baumann *et al.* 2019). Nevertheless, there are still many circumstances and treatment sites where the advantage of protons appears to be marginal at best (Lee et al., 1994; Liao et al., 2016). Thus, it is debatable whether the dosimetric advantages of proton therapy are clinically significant for all treatment sites, warranting the various randomized clinical trials comparing protons and photons that are currently being conducted for sites such as breast, prostate, lung, and many others.

There is thus much that still needs to be done to fully exploit the physical advantages of protons. As such, this roadmap focusses on physics and biology aspects that are currently, or should be in the future, the subject of major research and development projects. Other aspects that are already clinical reality or are well on their way to being clinical standards (e.g. Monte Carlo based dosimetry for planning and quality assurance) will not be addressed in detail. Furthermore, as most centers will be treating with beam scanning in the near future, passively scattered proton therapy is not discussed, even if many of the innovations highlighted in this roadmap are independent of the delivery method.

The targeted audience for this roadmap are the readers of Physics in Medicine and Biology. Accordingly, except when relevant in the context, we are not discussing specific clinical applications of proton therapy. Similarly, although the health economics and resulting societal impacts of treatment with proton therapy is a highly interesting and controversial field, we have not included articles specifically related to this or other societal impacts. With that said of course, many of the topics discussed here, such as efficiency gains and identifying those patients most likely to benefit from reduced side effects or improved tumor control with proton therapy, would be expected to reduce overall health care costs.This roadmap instead highlights the current state and future direction of proton therapy from the physics and biology aspects, in which we have categorized the articles into four different themes, “improving efficiency”, “improving planning and delivery”, “improving imaging”, and “improving patient selection”.

Improving efficiency

Proton therapy is a currently expensive treatment modality. Nevertheless, the cost of a proton treatment is expected to decrease with increasing number of facilities, and many developments in accelerator technology are focusing on lowering initial investments when acquiring a proton therapy facility by providing single room treatment facilities or even facilities without a gantry. Extensive work is being done also on improving beam delivery efficiency to reduce operating costs. These developments should of course not compromise the achievable dose conformity.

As such we have four roadmap contributions dealing with treatment efficiency; “Cost reduction by optimizing accelerator technology”, “Technology for delivery efficiency”, “Delivery technology”, and “Efficient treatment room utilization”. While not directly evident, roadmap contributions in other sections such as those concerning the biological effectiveness of proton beams as well as biomarkers may also contribute to improved cost effectiveness in the future. For instance, identifying patients most likely to benefit from reduced side effects or improved tumor control (based on tumor genomics) with proton therapy would be expected to reduce health care costs for society overall.

Improving planning and delivery

In comparison to IMRT or VMAT, there are typically many more degrees of freedom for modulation in proton therapy, due to the 3-dimensional distribution and application of individually weighted Bragg peaks. These additional possibilities are only just beginning to be explored, and much can still be done in the treatment planning process to best exploit these possibilities to improve treatment precision and accuracy. On the other hand, tissue deformations can significantly affect proton ranges in the patient so that proton therapy is generally more affected by intra and inter-fractional anatomy changes. Reducing uncertainties is thus a key research theme in proton therapy physics, as is the proper quantification, monitoring and reporting of uncertainties. Adaptive therapy has a higher potential for clinical impact in proton therapy compared to conventional radiation therapy. Uncertainties also exist in the biological effect of proton beams. As uncertainties can never be eliminated entirely, optimization techniques are being developed to reduce their clinical impact.

As these topics are currently researched heavily, there are seven roadmap contributions in this category: “Uncertainly precise – uncertainties in proton therapy and how to tackle them”, “Treatment planning”, “Development of robust planning”, "Adaptive therapy to account for daily anatomy and range variations”, “In vivo range verification”, “4D planning and delivery”, and “Considering the relative biological effectiveness of protons”.

Improving imaging

Modalities for pre-treatment diagnostic imaging are impacting all radiation therapy modalities. Even though originating in proton therapy in the 1960s and 70s, in-room imaging is currently more advanced in conventional radiation therapy. It is expected to make a bigger impact in proton therapy because of dose deposition uncertainties warranting treatment monitoring more closely but also because of dose-shaping capabilities with proton therapy that make small corrections both necessary as well as achievable. Furthermore, there are various efforts to improve tissue characterization for dose calculation in adaptive workflows.

There are two roadmap contributions about “Advances in imaging for proton treatment planning” and “Image guidance”.

Improving patient selection

There is an ongoing discussion about the necessity for randomized clinical trials to show a significant advantage in outcome when using protons in favor of photons. It is likely that for specific sites, proton therapy might be advantageous only for a subset of patients and model based trials to stratify patients into randomization have been suggested and are already being implemented at some centres. This raises the question about the applicability of dose-response models developed from photon treatment outcomes. Additionally, in the era of precision medicine, patient selection based on biomarkers is playing an ever-increasing role. We are just starting to scratch the surface of identifying sub-populations for (proton) therapy based on biological/genetic fingerprints. This has to be understood also in the context of (systemic) treatments prescribed in addition to radiation therapy. Indeed, maybe the most important areas for progress in proton therapy may lie in improving our understanding of differences in biological responses to proton vs. photon treatments. In areas such as predicting biological response based on genomic features, very little is known. Many of these developments are not necessarily specific to proton therapy. As such roadmap contributions about “Selection of patients for proton therapy”, “Outcome modeling for proton therapy”, “Biomarkers in proton therapy”, and “Systemic effects of proton therapy” have also been included.

Summary

Research and development in proton therapy is a topic of increasing interest in radiation therapy physics, medicine and biology, with the number of research articles about proton therapy greatly exceeding the number of photon therapy related manuscripts when considering the tiny number of patients under treatment. How this will develop in the future is the subject of this roadmap, which collects the opinion of leaders in the field and their vision on how this treatment modality will advance in the near future. As such, there are many personal opinions contained in this article, and opinions that not all readers will necessarily agree with. But that of course 'is the nature of the beast' when different experts are asked to take a look into the future. In addition, in order to catch a true 'snap shot' of current thinking, other than providing broad titles to the different contributors, we deliberately avoided providing any detailed guidelines on content, to not restrict their creative thinking and writing. Similarly, the contributors were not provided access to other contributions before submitting to the roadmap collection. As such, there are inevitable overlaps between some contributions, which we believe only enhances the article. If a topic is mentioned more than once, and completely independently by different authors, does this not add an important, and not to be ignored, emphasis to that point?

Part 1: Improving efficiency

Cost reduction by optimizing Accelerator Technology

Marco Schippers

Introduction

For routine clinical application of proton therapy, the cyclotron, synchrotron and synchrocyclotron will be the most commonly used accelerators in the near future. Although some developments are still aiming at a technical improvement, in general, these accelerators are considered to have reached a mature state, and that they have been developed sufficiently for their application in proton therapy. Therefore, in the coming years most improvements of these machines will be focussed on a cost reduction of the manufacturing and service. A reduction in size of the accelerator is regarded as a key issue in price reduction by the commercial suppliers of proton therapy accelerators. In parallel to these industrial developments, one is also working on a proton therapy application of recent accelerator developments in various research institutes and laboratories. After discussing the developments in synchrotrons and cyclotrons, these will be summarized shortly.

Synchrotron

Since the first phases of proton therapy, synchrotrons have been used and have been further developed specifically for this application. Proton-synchrotron accelerator systems are composed of a proton source and a linac (linear accelerator), which injects the protons into the synchrotron ring for acceleration. The synchrotron ring consists of several bending magnets and magnetic lenses. In the RF cavity, which is also mounted in the ring, an oscillating electric field is generated to accelerate the protons. The ring has a typical diameter of 6-8 m and the injector has a length of 6-10 m. The maximum number of protons that can be injected into the ring is limited (in the order of 10^9-10^{11}) but this number increases with the injection energy. A higher filling of the ring is still an important research topic, since for the application of one field at the patient, one typically needs 1-3 fillings and acceleration sequences (Hiramoto et al 2007). Therefore, a higher filling of the ring would reduce the treatment time considerably. The beam extraction process in a synchrotron for proton therapy, has been improved by the RF-knock-out technique (Hiramoto et al. 2007). With this technique the beam shape and intensity remain more constant during the extraction of the beam, which is of great advantage in controlling the dose application

procedure.

The most important cost drivers that are specific for each synchrotron type, are the ring diameter (i.e. the amount of magnets and their strength), the proton source, the injection system (injection Energy) and the RF system. Cost drivers related to the synchrotron are the footprint, systems to match the beam shape to the gantry angle and the ring filling and ramping time, which determine the averge dose rate at the patient (i.e. treatment time).

Smaller (and thus cheaper) synchrotrons, with diameters down to 5 m have been developed in the last decade (Wang et al 2011, Umezawa et al 2015). Also, the footprint of several synchrotron facilities has been reduced by optimizing the layout of the ring, proton source and injector and by combining the proton source and first acceleration steps (Vretenar et al 2014). A further cost reduction has been achieved by reducing the number of synchrotron elements and the differences between the individual magnets in the system.

A very significant improvement has been achieved in one of the synchrotrons for carbon therapy, by enabling a reduction of the beam energy during the beam-extraction phase (Iwata et al 2010). This is of optimal benefit for the necessary energy variations to cover the target in depth. This development, which is being implemented in some proton synchrotrons as well, can reduce treatment time by 30% in synchrotron facilities (Iwata et al 2010). Another development shortening the treatment time, is expected from an increase of the ramping speed of the synchrotron magnets (Trbojevic et al 2011). Although similar important improvements in facility operation are expected soon, no substantial facility size reductions are expected in the near future in facilities driven by a synchrotron. However, developments are continuing and these will optimize the synchrotron operation and yield a gradual cost reduction.

Cyclotron and synchrocyclotron

Since the last 25 years also cyclotrons are commercially available for proton therapy. These are single magnet machines, with a typical diameter of 5 m and a weight of 200 tons, which accelerate protons to a fixed energy. With a degrader followed by an energy selection system, all necessary lower energies can be obtained in a fast procedure. During the last decades important technical developments have been implemented into cyclotrons for proton therapy, so that several types of cyclotrons can be achieved nowadays. The differences in cyclotron costs are mainly related to differences in its size or mass (i.e. the amount of iron), superconducting (SC) coils or not, the RF system and the hardware and control of beam-quality determining components. Other cost drivers related to the cyclotron are the energy selection system, shielding and activation.

To reduce the size of a cyclotron, a stronger magnetic field is needed. This is only possible by using a superconducting magnet. The first SC cyclotron in proton therapy (Schillo et al 2001) has a diameter of 3.5 m and a weight of 100 tons. Further developments have enabled even stronger magnetic fields. Very small so called “synchrocyclotrons” of only 30-50 tons and a diameter 1-2 m, have been produced and taken into clinical operation in the last decade (MEVION 2019, IBA 2019). As expected, this has led to a significant reduction in the price of a cyclotron. For one type of these cyclotrons, its mounting on a rotating gantry (MEVION 2019) has decreased the facility footprint significantly.

However, contrary to the traditional “isochronous” cyclotrons (either with normal or with SC magnets), providing a continuous proton beam, the very small synchrocyclotrons can only operate in a mode with a pulsed proton beam. Their maximum pulse rate of 1 kHz imposes limitations on beam intensity (i.e. dose rate), so that one cannot have very short treatment times. Although the average beam intensity is limited, during the pulse the beam intensity can be quite high. At several sites this has be used for experiments in which small volumes have been irradiated with the very high dose rate in a pulse. Also, the expected very beneficial dose delivery techniques used to provide continuous pencil beam scanning,

are not possible with the pulsed beams from these synchrocyclotrons. To prevent these limitations and to reduce the costs related to the facility footprint, several companies now offer a single-room facility with a compact arrangement of a gantry with an isochronous cyclotron, providing a continuous, well controlled beam intensity.

In the field of SC cyclotrons, studies have also been started to design a synchrocyclotron with a magnet that has no iron yoke (Radovinsky 2014). This would reduce the mass of a cyclotron by a factor 10. However, since these ideas are still at an early design stage, no estimates on price and availability can be made yet.

Other accelerator types

Novel proton acceleration concepts based on e.g. lasers are being investigated. In laser based accelerators (Zeil et al 2013), major topics one is working on are: a very high beam power, a reasonable short repetition rate of the laser pulses, a sufficiently high proton energy and the energy spectrum of the protons created by the laser.

Other developments are focussing on a beam optics concept of fixed magnetic fields and alternating magnetic gradients. Both in accelerators) and in some gantry designs, one is applying a beam optics based on strong magnetic fields of alternating polarities and gradients (Sheehy 2016 and Trbojevic et al 2007). This has the advantage of large energy acceptance. Much effort is put in the construction of the tight packing of the very strong magnets of opposing polarities in a gantry design and a reduction of the power of such a Fixed Field Accelerator (FFA). This accelerator is based on such a beam optics of a ring of magnets with fixed fields having alternating strong magnetic gradiens. It is a synchroton like accelerator, but with fixed magnetic fields, similar as in a cyclotron.

The first linac for proton therapy has been developed from ideas used in high-energy physics and is almost ready for installation at a clinical site (Degiovanni and Amaldi 2014). An important advantage of a linac would be the possibility for rapid energy changes for range modulation. In a linac one can simply switch off or change the power in one or more acceleration cavities.

Although these developments are very important, for many of them still many steps have to be made before they are ready for implementation into a clinical facility. In addition to that, it is not clear yet, how much these developments in new acceleration techniques, will help to reduce the costs.

Conclusions and outlook

A brief overview of the most well known developments in accelerator technology has been presented in the context of a potential cost reduction of accelerators in proton therapy. Several options seem to be possible, but more dramatic changes are needed for a major cost reduction. And, since experience has shown, that major steps in proton therapy need approximately ten years from first trials to introduction into the clinic, it is expected that a dramatic, say 50%, cost reduction of proton therapy will not be reached in the near future.

Apart from the possible lower costs, it is important to consider the effect of the new techniques on the treatment possibilities. For each new technology, it should be verified whether the dose distribution delivered provides comparable quality to that currently available in proton therapy. Compromises taken to reduce the cost should not be accepted when this cannot be guaranteed. For the time being, the higher quality of the proton treatments is the only important reason to be competitive to other treatments. Accelerator related properties like intensity, pencil-beam size, energy spectrum, stability, reproducibility, time structure and the time needed to change a parameter, are the most relevant to consider in this respect.

Nevertheless, already now many successful developments in accelerator technology are available in commercially available facilities. Some of these are focusing on the lower initial investments when acquiring a proton therapy facility with only one treatment room. Single-room facilities will offer opportunities in certain cases, but it is not clear in general, whether single-room facilities will make with proton therapy treatments cheaper.

At present it is encouraging to see, that accelerator developments, such as smaller accelerators, facility size reduction and faster treatments, are entering into clinical facilities and are contributing to a reduction of the treatment costs. Next steps in cost reduction can only be achieved with further research in accelerator physics.

Technology for delivery efficiency

Jacob Flanz

Introduction

The spatial distribution of a beam from a particle accelerator is not normally a conformal match for the desired target. Therefore, one must direct the beam trajectory and 'spread out' the beam transversely and longitudinally (in depth). In doing so, one attempts to optimize the 3 dimensional distribution and in some cases a 4 dimensional distribution, the latter including the time dependence of beam delivery relative to patient motion (see article on "4D planning and delivery"). A key goal is to deliver a physical dose distribution consistent with a predetermined treatment plan. This treatment plan includes specifying the direction that this spread out beam should enter the patient.

For decades the main delivery modality was that of beam scattering (Koehler et al 1977). This is accomplished by scattering the beam with various types of physical devices in the path of the beam. Sometimes this is done passively enabling the entire volume of the dose to be delivered instantaneously and in some cases it has more dynamic elements such has range modulator wheels and beam current modulation, which can deliver the full volumetric dose in a fraction of a second. The beam delivery modality which has evolved to be the more desired and soon-to-be the most prevalent is that of beam scanning (Pedroni et al 1995) wherein the unmodified accelerator beam distribution is transversely scanned magnetically and the beam range is controlled by modifying the beam energy both of which have a finite time dependence. This beam was originally delivered from a fixed angle beamline, but then proton and heavy ion gantries were developed. These added needed (at the time) flexibility in beam direction as well as considerable expense.

For the purposes of this section, the word "efficiency" is interpreted to mean efficient in cost, time and treatment efficacy.

Status

Most of the modern facilities are designed to use particle beam scanning with rotating gantries. Most have been constructed to deliver a dose rate of about 2Gy per liter in a minute. Scanning beams hold the promise to deliver the most conformal physical dose distribution, however the ultimate dose distribution possible according to the laws of physics is still not achieved as a result of certain constraints and limitations. Recently, different beam delivery methods are being re-explored, such as mini-beam ribbon (Peucelle et al 2015) and FLASH (Mazal et al 2020) (see article on "Treatment planning") irradiation. These modalities may require revised beam delivery parameters including much higher dose rates.

Current and Future Challenges

This chapter focuses on the system components used to direct the beam to the patient including the beam spreading technology and the gantry. The challenges to be addressed here are specific to these components. Elsewhere, issues of localization and stopping power uncertainties will be addressed. Given the current beam delivery implementations, the necessity to address organ motion results in applying methods that include: Gating, Repainting and Beam size adjustment. The current systems are capable of these techniques. However, their design may be constrained to avoid the fundamental issues that would address the key challenges of the future. These challenges include:

- Reduced system cost, and
- Faster, accurate and safe beam delivery

The beam scanning delivery technology involves informing the system of the desired location and dose to be delivered in real time. If one knew precisely where the target was at any given time, the equipment technology is capable of producing and delivering a beam to that location. However, treatment planning has not yet reached the capability to calculate and transfer real time adaptive plans based upon the dose delivered with real time imaging (see articles on "Treatment planning", "4D planning and delivery" and "Adaptive Therapy"). Therefore, one would first consider pre-planned delivery options.

Delivering a 3D dose distribution in a time period small compared to organ motion would be a fundamental solution to handle the organ motion challenge. Currently, on the average, it takes on the order of a minute to deliver the volumetric dose required by the treatment plan (see article on "Delivery Technology"). This is comprised of two seconds or less to change the beam energy, each time it is required, and the time to paint a given range layer which is about, on the average, a second. Therefore, 30 layers will take about a minute. Some facilities are capable of faster delivery, such as 0.1 seconds to change energy. However even that amounts to more than 3 seconds total for just the energy changes, not short compared to the period of organ motion (respiratory or cardiac). Scanning dipoles exist with the capability of moving the beam at frequencies of 100 Hz (although the slowest ones move at 3Hz), and for spot scanning the settling time of the magnet/power supply combination can be as large as 5msec per spot (which, for 40x40 spots, could result in a 'dead-time' of about 8 seconds per layer). Furthermore, FLASH beam delivery requires dose rates of >40 Gy/second. It's not exactly clear what the beam delivery implications will be for this technique. Is that dose rate in the distal layer only sufficient, or is it required for the full volume and is there a time dependence, as in painting the volume, to the effect? Another aspect of this challenge of increasing the speed of the beam delivery are the commensurate issues of accuracy and safety in delivering the beam. One expects a dose delivery accuracy of better than 2%. Currently Ionization chambers (IC) are predominately used (in fact they are legally required in most countries). These systems may take 100usec, on the average, to detect and record the dose delivered. Therefore, there is always a delay and it is essential that the dose rate is such that the dose tolerance should not be exceeded in the time it takes to detect it. This results in a limitation of the beam current to fractions of a nano Ampere and results in dose rates that are currently used. To increase the speed of the scan or beam delivery current a factor of 60-100, to address organ motion, or a lot more (for FLASH) would require advances in the technology. The challenges identified so far include:

- Speed of Scan
- Speed of Ionization Chambers (ICs)
- Speed of Energy Change

When considering the cost of a particle therapy facility one cannot compromise on safety. One desires to deliver the beam to the appropriate target location in a speed consistent with the target accuracy desired. One of the most expensive pieces of equipment in a particle facility is a gantry. The size, weight, fabrication and building structure for such a piece of equipment is probably the single largest expense in

the facility. Attempts to reduce the cost of this component include shrinking its size longitudinally (via superconducting magnets (Gerbershagen et al 2016) or corkscrew geometry (Koehler 1987), or reducing the lateral extent by limiting the rotation range to about 180 deg (Pedroni et al 2004). However, while the superconducting option can reduce the cost of these systems for heavier Ion facilities, it does not reduce the facility size significantly for proton centers. The largest cost reduction would come from the elimination of the gantry mechanical component.

Advances needed to meet the challenges

If one looks again at the key challenges, perhaps one can identify the most appropriate way to address them, given what is known now or can be imagined now.

Speed of Scan: Conventional magnets exist that can move the beam quite rapidly. The issue is how big they need to be, which is related to the size of the field extent and the distance from the magnets to the target. Without a gantry (solving two problems with one solution) the distance can potentially be larger and the magnets smaller, with lower inductance enabling reduced dead time and faster current changes. However the dose rate must be sufficient to deposit the desired dose in the time, and while most accelerators can do this, the existing ICs used cannot.

Speed of Ionization Chambers: Smaller gap, higher voltage systems are required, which may be possible since the scanning beam modality requires lower beam current than was necessary in the scattering systems. Or perhaps one can replace these with alternative options. For example, knowledge of the beam's incoming trajectory together with the magnetic field should be capable of accurately predicting the position of the beam on target, thereby avoiding the need for additional redundant instruments such as Ionization chambers. Other instruments for counting charge such as toroids or scintillators might be considered to replace ionization chamber dose monitors. This may necessitate modification of the regulations.

Speed of Energy Change: This is perhaps the most technologically difficult issue. The contributions to this time include the accelerator (for some systems) and the beam line. Synchrotrons are now starting to use 'multi-energy' extraction (Younkin et al 2018), and cyclotrons rely on a degrader with the magnetic energy analysis system. One method is to eliminate a beam line (Prusator et al 2017), which is possible for a single room system. Otherwise the magnetic beam line system must be designed to enable faster energy changes (e.g. on the order of 0.02 seconds). This is possible from an engineering point of view, but may increase the system costs and commissioning complexity. Feedback and feed-forward systems are possible, some examples of which have been implemented.

System Cost: The simple, and yet not widely accepted answer is to eliminate the gantry. With decades of experience using gantries, given the convenience of setting the beam trajectory and patient positioning, it is hard to conceive of this disruptive change. Prior to gantries one used fixed beam lines for treatment and experienced difficulty in achieving the desired beam angles relative to the patient orientation. However, one needs to consider the modern systems, with scanning beams, robotic positioners, more flexible imaging and flexible immobilization. Scanning beams are highly conformal, and that means that they are capable of delivering a conformal dose with fewer and more limited field angles. Studies have shown that fewer non-coplanar field geometries are necessary (Yan et al 2016). The issue is then what is the range of patient orientations that are necessary and how to ensure that the patient anatomy is in the appropriate position for these geometries? Robotic positioners can orient the patient in flexible positions (upright, lying down and forms of sitting) and in-room imaging is capable of verifying a patient's position in multiple orientations, if that is needed in the course of one fraction (e.g. orientable CTs, swing arm CBCTs). Comfortable and easy to use immobilization is perhaps the element most lagging in this equation. Developments of this are underway.

Concluding Remarks

The evolution of beam delivery technology is sometimes done adiabatically. While the change from scattering to scanning was, in fact, a disruptive technology, the former has slowed the evolution of the latter. Sometimes one has to identify the issues very clearly and boil them down to their essence to, in this case, realize that one needs to use an appropriate imaging technology and immobilization to enable a gantry-less solution and deliver a beam very quickly. These are the technologies that will deliver the largest gain. Probably the most important development to achieve these goals is improved beam instrumentation, or a revisiting of the type of instrumentation that is required. Perhaps it may be noted that there is another goal relevant to beam delivery technology, which at first thought may appear separate from the considerations identified above, but upon further reflection may become the magic bullet of radiotherapy. If this "FLASH" radiotherapy turns out to be shown to be favorable in humans, then the imperative to address the fast dose delivery with charged particle imaging will enable further significant reduction of side effects to healthy tissue while enabling delivery of the dose in a time scale short compared to motion and delivered to the correct location and depth as given by direct charged particle imaging. It is critical to direct the evolution of the technology to address the current challenges and finally achieve what charged particle therapy has ultimately promised for the past half century. And this can all be done with less expense if one removed the rotating gantry.

Delivery technology

Hakan Nystrom

Status

One of the areas where a significant cost reduction in Proton Therapy (PT) seems possible and achievable is in the potential of increased efficiency (see article on "Efficient Treatment Room Utilization"). As today, the allotted treatment times are typically significantly longer in PT than in conventional, linac-based treatments (Suzuki *et al* 2016).

There are many reasons for the longer treatment times in PT, e.g. on average more complicated treatments with several fields with/without the use of range shifter, a higher need for imaging due to the need for rapid adaption and the sharing of the accelerator with several treatment rooms. Despite the increasing installations of "single room" solutions in recent years, multi-room facilities with anything from two to five rooms still dominate. Sharing the beam means that one or two (or even three) rooms may be before you in line when you are ready to treat. A slow field delivery time hence also affects all those rooms waiting for the beam and any second gained by faster beam delivery will be multiplied by the number of rooms waiting. Waiting time may also deteriorate the treatment since the patient may move during this period and call for additional imaging or position verification. The cost for a treatment, or fraction, scales more or less linearly with the time the patient spends in the treatment room and reducing the length of the time slot, without compromising the quality of the treatment, will consequently reduce the cost to the same extent.

Advances in Technology to meet challenges

Looking deeper into the technological solutions for spot scanning facilities today, one easily gets the impression that the concept of treatment efficiency has largely been neglected in the design process. The different accelerator types (cyclotrons, synchrotrons and synchrocyclotrons (see article on "Accelerator Technology") all have different characteristics and will therefore in the following be partly treated separately, although the main focus will be on (isochronous) cyclotrons, since it is the most used type of accelerator in PT.

There are three main parameter ruling the time it takes to deliver a given treatment field; the spot delivering time, the time between spots and the time it takes to change the energy (see article on "Technology for delivery efficiency"). A cyclotron produces a continuous beam (ignoring the RF frequency pulses) and to deliver a spot with a given number of protons (or MU´s), the beam is turned on, the dose is monitored by a dose monitor and turned off when the pre-set value is approached. This means that the signal from the monitor chamber must be tracked and analysed in real-time and to achieve a high degree of accuracy, a certain time, typically a few ms, is needed. Prior to irradiation, an estimate of the needed beam current is done by the system to ensure the spot duration not being too short. With faster electronics and analytical capacity, this could probably be somewhat reduced in the future. However, and more importantly, the possibility to adjust the beam current from the accelerator *between* consecutive spots is of crucial importance. In some systems this can be done, meaning that all spots have (more or less) the same duration of a few ms, whereas in other systems, the beam current is calculated to ensure that the smallest spot (with the smallest number of MU's) will be long enough, and the modulation of the spot intensity over each energy layer, is done by prolonging the spot duration with the same beam current. In the latter case, the time to deliver a field will typically be at least twice as long, as if the beam current was modulated (Müller and Wilkens 2016). The actual prolongation depends on the amount of modulation the spots in the field have and on the minimum number of MU's allowed, but it's important to realize that even in single field optimized treatments, there is a significant spot modulation, also within each energy layer.

In a synchrotron, the situation is similar in this respect. The accelerator is loaded with a certain number of protons and then the protons are extracted in "spills" and the accelerator is filled up again. During a spill, the beam can be viewed as continuous and the same principles as for a cyclotron can be applied.

A synchrocyclotron represents a completely different situation. Here the beam is pulsed with a beam duration of only a few μs per pulse, pretty much like in a linac. Hence, the pulse duration itself does not really contribute to the beam delivery time, but since the number of protons (or MU's) delivered in a pulse is ruled by the upfront loading of the cyclotron, rather than by the reading of the monitor chamber, more than one pulse is needed to build up a spot. This is due to the fact that the number of protons in a pulse cannot be predicted (or determined) at the ion source level to the accuracy needed in PT. The important factor that rules the actual beam delivery efficiency then becomes the pulse repetition frequency (PRF), which scales more or less linearly with the efficiency. For the present and most widely spread synchrocyclotrons, the PRF is between 500 – 1000 Hz; increasing the PRF will directly reduce the beam delivery time.

The second parameter determining the beam delivery time is the time between spots; the time it takes to move from one spot position to the next. This is mainly governed by the speed of the scanning magnets. When the magnetic field is to be changed in an electromagnet, eddy currents generated in the yoke of the magnet reduces the speed of which this change can be done. A way to counteract this effect is just to wait until the magnetic field has settled and stabilized. If this time is to be reduced, an approach could be to predict the spot position effect due to this and compensate for that, and in that way allow a reduced settling time (Psoroulas *et al* 2018). Another method is to introduce "line-scanning". With this approach the pencil beam is continuously moved in lines over the area to cover. Modulation of the beam intensity can either be made by modulating the beam current, or by keeping the current constant but modulating the speed of the scanning magnets, or both (Klimpki *et al* 2017). A prerequisite is that the beam current is stable enough and this may present a challenge for synchrotron-based systems. This method can be made significantly faster and solves, at least to some extent, both the problem of spot duration and the dead time between spots, but is demanding in terms of beam delivery monitoring and validation. To perform line scanning, a continuous, rather than pulsed beam, is needed. Hence, line scanning cannot be

performed with a synchrocyclotron.

The third parameter is the time it takes to change the energy from one layer of spots to the next. For most modern cyclotron based systems, this time is around one second, or slightly more. Large efforts have been done to reduce this at some centres, e.g. at the Paul Scherrer Institute in Switzerland (Klimpki *et al* 2018). The main purpose of this is to better manage organ motion and e.g. to make volumetric re-painting feasible, but without doubt, this parameter also influences the overall efficiency.

In synchrotrons, each energy layer typically demands a spill of its own. This means that even if the number of spots within a certain energy layer is small, the accelerator has to go through the whole acceleration cycle, which takes typically several seconds. For details of the timing of synchrotrons in a clinical context, see e.g. (Gelover *et al* 2019; Boria *et al* 2018). Ways to improve this has been done by e.g. by decelerating the beam during a spill (Iwata *et al* 2010; Younkin *et al* 2018) and with the so-called multiple energy extraction method, beam delivery time can be reduced by a third for typical clinical fields. Another approach to speed this up can be to decrease the "dead time" between the spills by increasing the ramping speed of the magnets (Trbojevic *et al* 2011).

Once a PT system is installed, most of the above parameters are given and cannot (easily) be improved or changed. If the time to deliver a spot and to move to the next position cannot be changed, the actual number of spots in a given energy layer can (van de Water *et al* 2019). Larger spots mean that larger distance between spots can be applied, and hence fewer spots can be used without causing a dose ripple (for further relevance of this, see also article on "Treatment planning for pencil beam scanning proton therapy"). Fewer spots with a larger number of protons in each spot, is associated with significantly reduced beam delivery time. The exact reduction is dependent on several parameters such as available beam current and is also different between different delivery systems. Several PT vendors offer different "spot ID's" by the introduction of a scattering foil in the treatment head (nozzle). The price to pay for larger spots is a larger penumbra and somewhat reduced modulation possibilities and consequently this approach has not become a standard tool in most clinics. A way to overcome this would be to allow different spot sizes within the same energy layer, e.g. smaller spots at the edges and larger spots in the central part of the field. To make this possible, rapid changes of the spot sizes are needed which is difficult with a scattering foil. With present systems the foil is either in or out during the complete field. Attempts to widen the beam with magnetic defocussing instead of a scattering foil have been explored but is not widely available. However, such an approach would also have the appealing quality of designing the actual spot size individually for each energy, which cannot be done with a limited number of scattering foils. Yet another approach to solve the penumbra drawbacks of larger spots is to combine the scanning with a collimator. Advanced solutions are required in order not to detract the other obvious advantages with the spot scanning technology. One such commercially available solution is the so-called Hyperscan from Mevion (Kang *et al* 2018).

The equivalent of spot size in the depth direction is the initial energy spread of the proton beam. Typically this is around 1 %, resulting in a very steep distal fall off of the Bragg peak. Although this is often seen as an advantage with PT, the sharpness of the peak may be too sharp, in particular at the low energies, to be clinically useful (considering e.g. range uncertainties) and results in very small energy steps and many energy layers to avoid a dose ripple. One way to intentionally introduce an increased energy spread and hence soften the Bragg peak is to apply a ridge (or ripple) filter (Printz Ringbæk *et al* 2017; Grevillot *et al* 2015). With a proper design, virtually any shape of the Bragg peak can be obtained. But just as with scattering foils to broadening the spots, a ripple filter is yet another mechanical device to be introduced into the beam line, typically by manual handling, with limited possibilities to change between energy layer or, even more so, from one spot to another. If the gantries could be designed with a wider momentum spread acceptance, the energy spread could be determined further up-stream in the beam line

and in cyclotrons there are already a momentum slit in the energy selection system that could be used for this purpose (Hsi *et al* 2009; Nesteruk *et al* 2019). But again, the actual acceptance of the beam line is given by the original optical design and cannot (easily) be retro changed. The longer it takes to change the energy of the proton beam, the more important it gets to optimize the number of energy layers used. This aspect can be introduced in the treatment planning optimizer and significant energy efficiency gains have been demonstrated (Kang *et al* 2008; Cao *et al* 2014; van de Water *et al* 2015). An exception to the above situation is the gantry-mounted design by Mevion where no energy selection is present and the sharpness (or lack thereof) is the same independently of energy.

In conventional radiotherapy, the move from IMRT to volumetric modulated arc therapy (VMAT), led to a significant efficiency gain. A similar development has been demonstrated also for PT (Li *et al* 2019), but since the difference in dose distributions are greater than in the photon case, it is probably too early to know if proton arc therapy will become a standard delivery tool in the future. In IMRT a relatively large number of fields are typically used, meaning that the dose is distributed to larger volumes. This effect is even larger in VMAT, yet smaller than the difference is between IMPT (where relatively few fields are used) and PT arc therapy.

This far the beam delivery time has been discussed. Obviously the beam-on time is just a small part of the overall "patient-in-the-room" time and an increased "Dose rate" may only have a limited effect on the overall efficiency. But for many of the systems a reduction by a factor of two or more for the beam delivery time seems realistic and for multi room systems, this could result in an improved efficiency of the order of 10 – 25%. If complex beam delivery applications are used, e.g. re-painting or gating for motion mitigation, the efficiency gain is even higher.

As mentioned above, a faster beam delivery time will have the greatest impact on multi room facilities, where the waiting time for the beam is an obvious limitation (see article on "Efficient Treatment Room Utilization"). But also the beam sharing system itself is of importance. Most systems have the possibility to choose a "priority" for their treatment, i.e. to choose whether or not to give the beam away between consecutive fields of a patient. To accept to give the beam away reduces the waiting period each time, but increases the number of room switches and increases the overall treatment time. Faster room switching, e.g. by allowing dedicated power-supplies to each gantry-specific magnetic component, rather than sharing those, and smarter scheduling tools, might reduce the problem. Future design improvements with the possibility to share the beam, i.e. deliver beam to more than one room at the time, may be possible, but this is technically complicated and will lead to increased equipment costs (Schippers and Lomax 2011).

Image guidance (IG) (see article on "Image guidance") is used extensively in PT and this obviously slows down the efficiency. One cannot argue for reduced IG as long as it improves the quality of the treatment leading to improved clinical outcome. However, IG in PT is often to a substantial part also used as a technical quality control to make sure the equipment, in particular the robotic patient positioner, is in the right position, rather than checking the positioning of the patient or the target. Poor accuracy and precision of the patient couches is still a problem and limited trust in the equipment leads to over-imaging and prolonged treatment sessions.

Manual handling of beam modifying devices, in particular range shifters constitutes a substantial source of inefficiency, in particular for installations where the range shifter cannot be remotely operated. To counteract this source of treatment prolongation, it is not uncommon with a sub-optimal use of the range shifter, e.g. to use it for all fields, even those where it's not needed, just to avoid the delay of manual handling, but with a deterioration of quality. Improved penumbra and better dose distributions can sometimes be achieved by splitting the fields and use the range shifter only for the energy layers it's really needed, but to apply this method in an efficient way, automation is needed (Francchiolla *et al*

2017). Remotely operated range shifters are urgently called for and it should not be an unsolvable issue also for existing clinics.

As discussed in a previous chapter (see article on "Technology for delivery efficiency"), gantries in PT constitutes a significant part of the investment. The gantries in PT are substantially larger and heavier than conventional gantries. As a consequence and for safety reasons the gantry speed is sometimes limited compared to the 1 RPM commonly encountered in conventional radiotherapy. Some systems also experience a "cork screw effect", meaning that the exact position of the gantry is depending on the direction from which the position is approached, i.e. clockwise or counter-clockwise. For some systems an "over-travel" is needed if the gantry is rotated from the wrong direction, meaning a further prolongation of the treatment session. The issue of heavy gantries may not be trivial to fix for existing gantries, but should be a parameter to consider when procuring a PT system. The over-travel issue, however, is expected to be solvable.

Concluding remarks

There are a number of reasons why PT is so much slower than conventional radiotherapy. To a significant degree this could be improved in future designs by ensuring a faster beam delivery time, faster and more reliable gantry designs and maybe even by the possibility to share the beam in a smarter way in multi room facilities. For existing facilities, the options are limited when it comes to the beam delivery technology, but there are some obvious issues that should be promoted, e.g. remotely controlled range shifters, the possibility to modulate the beam current in-between consecutive spots and multiple energy extraction for synchrotrons.

Efficient Treatment Room Utilization

Chris Beltran and Keith Furutani

Status

Efficient utilization the Particle Treatment room for patient treatments and quality assurance will reduce the overall cost of treatments and improve patient care. The overall financial impact of a facility is not only the upfront equipment and building expense, but in the long run it will be efficiency of daily patient treatment and room occupancy that dictates true cost of operation and patient treatment cost. In this section, we will assume sufficient demand to fully occupy a given facility; therefore, details and method of effective demand generation will not be discussed here but is a crucial concept in cost reduction.

There are four main time components for patient occupancy in the treatment room: 1) patient and therapist entering and exiting the treatment room; 2) immobilization and image guided localization; 3) beam on time; 4) equipment preparation (gantry and table rotations and beamline settings). The other major room occupancy is the quality assurance (QA) procedures that must be conducted. This includes daily, monthly, annual machine QA and patient specific QA (PSQA).

The current status for room patient room occupancy is as follows: 1) 4-5 minutes to enter and 4-5 minutes to exit the treatment room; 2) 4-5 minutes for immobilization and 3-5 minutes for image guidance; 3) 2-3 minutes of beam on time; 4) 3-6 minutes for gantry rotation and beamline settings. This gives a total of approximately 20-30 minutes, which is currently difficult to achieve in most centers. These are just approximations, as some treatment sites may take longer. Many current proton facilities reserve 20 to 45 minute time slots for the average patient, while most photon facilities reserve only 15 minute time slots, this incudes facilities with have both proton and photon capabilities.

Current and Future Challenges

Current challenges include the fact that particle therapy is particularly sensitive to small anatomical changes, which can erode the quality of the target coverage and normal tissue sparing (see article on "Uncertainties"). This makes the immobilization and image guidance step extremely crucial (see article on "Image guidance"). A lot of time is spent in the image guidance step, as the data provided is not always fully informative as to the acceptability of the current patient setup. For example, if the image guidance currently shows partial sinus filing in a head and neck plan that had none during simulation, what is the compromise, if any, to the target coverage and/or normal tissue sparing? These types of changes are difficult, if not impossible, to account for with robust optimization planning techniques.

In the future, many treatment sites will move toward hypo-fractionation and/or incorporating some type of target motion mitigation technique to reduce the interplay effect (under or over dosing due to beam scanning motion relative to breathing motion). As these trends continue, the limitation in effective dose rate will become more pronounced. The current dose rate standard is approximately 1 to 2 Gy/min to a cubic target with a one liter volume; however, this dose rate is difficult to achieve with real targets. This limitation is mainly due to energy layer switching time, spot scanning time, and effective particle current at lower energies. For multi-room facilities is the additional limitation due to a finite field or course or room switching time. A typical room switching time is 20-45 seconds, given 120 fields a day and 30 seconds switching time this is an hour per treatment room that is "wasted".

The increase in hypo-fractionation will also increase the number of PSQA as the expectation will be to treat more patients in a given month and hence increase the PSQA workload. The current practice for PSQA in many centers is time consuming and with no change in efficiency will limit the total number of new patient starts in a given month.

Advances in Technology to meet Challenges

Many centers are beginning to adopt a log based/machine files approach to PSQA (Johnson et al 2019 and Belosi et al 2017). This is a first step to decreasing the amount of time the treatment room is utilized for PSQA and thereby freeing up more time for patient treatments. Specifically, a log based QA approach uses the data from the treatment delivery system to ensure proper delivery of the radiation. The cited references detail how this is done and quantifies the time savings. Another practice currently being implemented in some clinics is the use of direct shield doors. These doors open quickly and eliminate the need for a long maze; thereby reducing the time needed for patients and therapist to enter and exit the treatment room. While implementing advanced IGRT such as high quality CBCT is crucial, the particle gantry rotation speed remains an issue. Work is currently being done to increase the gantry rotation speed to from ½ rotations per minute (RPM) to 1 RPM. Other proposals suggest a closed design such that the 1 RPM restriction will no longer be an issue issue (similar to a TomoTherapy design). Research and development is also underway to improve the effective clinical dose rate. This will not only reduce treatment time, but may allow for minimization of the interplay effect. The goal is to allow a stereotactic field of ~200 cc to be delivered within one small breath-hold, ~5 seconds. Accelerators such as the VEMIC (Hori et al 2019) would allow high dose rates at all energies without the use of an energy degrading device. The time required for beamline settings, particularly in a multi-treatment room with one accelerator setup is being addressed twofold: first by having one accelerator support only one treatment room, and two by optimizing the time required to reset the beamline from room to room for multi-room systems.

In addition to the mechanical and control system improvements described above, much advancement is needed in the treatment planning realm. One method the treatment planning can aid in treatment room utilization is by optimizing the spot pattern to reduce the overall treatment delivery (see also articles on "Delivery Technology" and "Treatment planning"). However, the key improvement will be the realization of Real-Time Adaptive Therapy, which will require Real-Time PSQA that does not need to

occupy any treatment room time and is transparent to the end user. Particle therapy is, in general, more sensitive to setup and anatomical differences than is photon therapy (see article on "Uncertainties"). This sensitivity increases the time used during setup and image guidance. The use of efficient Real-Time Adaptive Therapy (see article on "Adaptive Therapy") can lead to decreased room time and increased dosimetric plan quality.

Concluding Remarks

As we can see from the previous section, there is no reason that in the near future we cannot have efficient treatment room utilization for both patient treatments and QA that will enable the cost of therapy to decrease while simultaneously increasing the quality and effectiveness of the delivered treatments. These advancements in technology are either currently being implemented in select clinics or are on the roadmaps of different vendors and/or facilities. The relative weight of each item to the efficiency gains is hard to assess as it depends on the details of the individual system, but these are items to consider and do a thorough investigation on when designing a future system. With these advancements, there is no reason that a patient time slot cannot be 15 minutes or less, similar to most current photon treatments.

Part 2: Improving planning and delivery

Uncertainly precise – uncertainties in proton therapy and how to tackle them

Tony Lomax

Introduction

Uncertainties are an inherent part of the radiotherapy process, but have been particularly highlighted in proton therapy. Indeed, there is hardly a conference or workshop in this field where 'robustness' (the corollary of uncertainty), in the form of tools for its evaluation or optimisation, is not a hotly discussed topic. In many ways, this is a very healthy development. On the other hand, are we in the community really putting our resources in understanding the most clinically relevant uncertainties? In this brief article, we will identify fourteen sources of uncertainties in the whole process of proton therapy, each one identified by a roman numeral. Based on this, we will propose a list of uncertainty issues that should be addressed in particle therapy in the next years, together with an estimate of their relative clinical relevance. These are summarized in table 1. Note, that the categorization and estimates of clinical relevance in the table, and indeed throughout this short article, are necessarily based on a very personal view which some may find controversial. As such, the author does not expect that all readers agree with the views expressed here. But I do hope that the sometimes provocative statements promote some debate.

Current and future challenges

Clinical uncertainties: Uncertainty raises its ugly head already at the time of diagnosis (or the missed diagnosis) of cancer (**I**). But even once a tumor is identified, it cannot always be stated with certainty what the histology of the tumor is, or even more, its stage of advancement and spread (**II**). Nevertheless, all these factors will have a substantial impact on the management of the disease, which from the point of view of radiotherapy means the definition of the total doses and fractionation scheme with which the tumor should be treated, as well as the size and form of the expected microscopic spread of the disease. Indeed, this delineation step has been well documented to be haunted by huge uncertainties and inter-clinician variability (Mercieca et al 2020, Apolle et al 2019, Aznar et al 2017) with the contours for the *same patient* varying by typically 3cm (Hausdorf distances) for some indications (**III**).

Biological uncertainties: At the most fundamental level, the above-mentioned clinical uncertainties are related to the underlying biology of the patient, their normal tissues and the tumor. In addition however, there are substantial uncertainties in the biological *response to radiation* of the patient and tumor (see article on "Biomarkers").

Perhaps, and as discussed in an accompanying roadmap article on the relative biological effectiveness (RBE) in this issue, the largest biological uncertainty is due to the inherent variation in individual sensitivity of patients to radiation (**IV**). In addition, there is considerable uncertainty in dose response at the cellular level, as typically characterized by the Linear-quadratic model. For this, tissue specific alpha-beta values are notoriously difficult to determine *in vivo*, and even the model itself is likely a gross simplification of the complex mechanisms of radiation damage at the cellular and organ scale (**V**) (Unkel et al 2016, Nagle et al 2018). Finally, and perhaps the most clinically relevant biological uncertainties, is our current lack of knowledge of the clinical response of tumors and organs to inhomogeneous dose distributions (**VI**).

All of the above are common to all forms of radiation therapy. For particles however, there is the additional uncertainty of their differential biological effect, typically characterized as an RBE. The variability of this is covered elsewhere in this issue, but in addition, there is mounting evidence that the fundamental differences of DNA damage by particles will lead to effects more complex than can be encapsulated in a simple relative value (**VII**) (Grosse et al 2014). Much still needs to be understood in this respect that could substantially affect how particles will be exploited in the future.

Positioning and anatomical uncertainties: Positioning and anatomical uncertainties are present for both photon and proton treatments. However, particularly for anatomical changes, proton treatments are significantly more sensitive to such changes than in conventional therapy. For instance, in addition to potentially deforming the tumour and surrounding normal tissues, more importantly for proton therapy, they can significantly affect particle range in the patient. Indeed, for many anatomical regions, uncertainties in the accuracy and precision of proton treatments resulting from time dependent changes of the patient themselves can be huge, and substantially larger than many other uncertainties (see e.g. Albertini et al 2008, Hoffmann et al 2017 and Nenoff et al 2020).

Such changes can occur either between (inter) or within (intra) fractions. For some inter-fractional anatomical changes, for example variable filling of internal cavities, weight loss/gain or tumor shrinkage/growth, substantial changes to target coverage can result (**VIII**) (Albertini et al 2008, Hoffmann et al 2017). *Intra-fraction* motion adds to this uncertainty cocktail, with both cyclical motions (e.g. breathing, heart beats etc.) (**IX**) (Grassberger et al 2013), as well as slower time-scale drifts of the patient anatomy and/or tumor (base-line shifts) (**X**) adding considerable uncertainty to the treatment (see article on "4D planning and delivery").

Delivery uncertainty will also occur due to the inevitable inaccuracy with which a patient can be positioned in relation to the treatment beam on a day-to-day basis (**XI**). This is a well documented problem, with many proposed solutions already available, ranging from the use of the statistically calculated planning target volume concept, through to plan optimization that also incorporates multiple set-up uncertainty scenarios (Unkelbach et al 2018).

Imaging uncertainties: Even without anatomical and set-up variations, there will always be an inevitable 'base-line' of uncertainty of the range of particles in the patient, simply due to the indirect imaging processes currently used for estimating *in vivo* range (**XII**) (see article on "Imaging for treatment planning"). For example, single-energy X-ray CT has been predominantly used for calculating proton range in the patient. In the community, such an approach is estimated to have an uncertainty of +/-3-3.5% (Paganetti 2012), although this will be lower in most soft-tissues, whilst being somewhat higher in

some forms of hard bone. The introduction of dual-energy CT has now decreased this to about the +/- 2% level (Wohlfahrt and Richter 2020). In the presence of non-biological implants such as metal teeth fillings and surgical stabilizations however, range uncertainties can be locally much larger, due to artifacts resulting from limitations in the image reconstruction processes when high-density materials are present.

Dose calculation uncertainties: Despite having sophisticated tools for designing, simulating and evaluating treatments either before (in the treatment planning process) or after (for outcomes analysis) treatment, the accuracy with which such systems can predict the point-to-point dose within the patient are limited, even if all the other patient related uncertainties are ignored (**XIII**). Although MC calculations are undoubtedly more accurate than analytical approaches, and will become increasingly useful as calculation times reduce (Qin et al 2016, Schiavi et al 2017, Ma et al 2018), their accuracy is ultimately limited by how well the patient anatomy is represented by the CT on which dose is calculated (c.f. *Positioning and Anatomical Uncertainties* above).

Machine delivery uncertainties: The final category of uncertainties considered here are those of the delivery machine (**XIV**). Briefly put, uncertainties in machine delivery are negligible in relation to the other uncertainties affecting fractionated particle therapy, at least if monitored and pro-actively corrected as part of a comprehensive quality assurance program. Nevertheless, there are undoubtedly areas for improvements in machine design and technology that can help to reduce patient related uncertainties, such as improved on-board imaging to help mitigate inter-fractional patient changes, as well as substantially reduced delivery times to mitigate the effect and magnitude of intra-fractional motions.

Uncertainty category	Source of uncertainty	Relative clinical relevance	Example research areas for uncertainty mitigation
I	Tumor diagnosis	5	• Improved physiological, functional and cellular imaging
II	Tumor staging	5	• Tumor specific bio-markers
III	Tumor extent	4	• Improved physiological, functional and cellular imaging • AI/ML supported automatic contouring
IV	Patient specific sensitivity	4	• Radio-sensitivity assays
V	Cellular response to radiation	4	• Pre-clinical in-vitro studies
VI	Organ response to radiation	4	• Organoid and small animal irradiations • Curative irradiation of spontaneous tumors in medium size animals • Multi-variate outcomes analysis
VII	*Differential biology – protons/X-rays*	*3*	• *Beyond RBE pre-clinical cell and small animal studies* • *Multi-variate outcomes analysis*
VIII	*Inter-fractional anatomical changes*	*3*	• *Proton compatible on-board imaging* • *Fast and automated plan adaption*
IX	*Cyclical intra-fractional changes*	*3*	• *Near real-time, on-board, 2/3D imaging* • *Gating/Breath-hold/re-scanning*

			• *Ultra-fast delivery*
X	*Systematic intra-fractional changes*	*3*	• *Near real-time, on-board, 2/3D imaging* • *Fast and automated plan adaption* • *Ultra-fast delivery*
XI	*Patient positioning*	*2*	• *Comprehensive robust planning* • *Fast and automated plan adaption*
XII	*Residual range uncertainties*	*2*	• *Dual energy/Photon counting CT* • *Proton CT* • *In vivo range verification* • *Comprehensive robust planning*
XIII	*Dose calculations*	*2*	• *GPU accelerated Monte Carlo*
XIV	*Machine delivery*	*1*	• *Improved position and dose monitoring* • *Faster monitoring, electronics and processing*

Table 1. A categorized list of uncertainties, together with a personal ranking of their relative clinical relevance. 5 is most relevant and 1 least relevant. Proton specific uncertainties are highlighted in italics.

Advances in technology to meet challenges

An overview off all the categories of uncertainties discussed above is shown in table 1, with a relative indication of the clinical relevance of each. Note, that this scale is not meant to be linear, and is also not meant to indicate that any area of research to mitigate these uncertainties is necessarily more important than any other. It just aims to put the uncertainties discussed here into clinical context. In addition, possible research topics for mitigating the categorized uncertainties are listed in the right-most column, with those where the solutions will be proton therapy specific highlighted in italics. As such, this table aims to provide a research and development roadmap for comprehensively reducing uncertainties in proton therapy. If successfully completed, these will substantially improve the quality and efficacy of what is an already a precise and successful treatment modality.

Concluding remarks

There are uncertainties related to every step of the proton therapy process, and eliminating them completely is impossible. However, through technological and methodological developments, improvements can be, and should be, made everywhere in an attempt to systematically reduce the uncertainty budget of proton therapy.

Treatment planning for pencil beam scanning proton therapy

Tony Lomax

Status

If the delivery machine is the heart of radiotherapy, then treatment planning is the brain. Whatever the capabilities of the beam delivery system, these can only be exploited to their clinical best by treatment planning systems that can fully explore the myriad of solutions to the treatment problem.

However, as PBS proton therapy has only recently become clinically mature, we have only just begun to scratch the surface of the possibilities of PBS proton therapy, and to go deeper, many developments in the techniques and tools of treatment planning are required. Note, as robust and biological (RBE) planning have dedicated sections in this roadmap article, in this section we will concentrate on other

areas for treatment planning development that need to, or will be pursued in the coming years.

Current and Future Challenges

One of the major characteristics of the treatment planning of proton therapy is its **flexibility**, where many solutions to the PBS planning problem provide superficially similar dose distributions to the target. As such, PBS proton treatments to the same case can vary enormously depending on the treatment planning system used, and the inputs provided. But this flexibility is a two-edged sword. On the one side, the use of different planning practices and tools at different institutes could lead to heterogeneous and perhaps contradictory clinical results, or make patient selection, when based on comparative planning exercises, inconsistent and potentially misleading (see article on "Selecting Patients for Proton Therapy"). On the other side, this flexibility is ripe for exploitation, for instance to substantially improve the quality or deliverability of proton therapy.

Another major issue for proton therapy is its sensitivity to **anatomical changes** of the patient throughout the treatment course (Szeto et al 2016, Hoffman et al 2017). Ideally, methods to estimate these effects should also be incorporated in the treatment planning process in order to best mitigate (see section on adaption), or record, their effects on the delivered treatment (see article on "Adaptive Therapy"). Indeed, the issue of **dose reporting**, in the form of three-dimensional distributions of the estimated dose delivered to the patient, is a crucial, unique and perhaps undervalued attribute of radiotherapy and the treatment planning process. For instance, from such data, it is possible to build biological models predicting treatment outcome with ever increasing sophistication (see e.g. Wopken et al 2014), but models, which, in the end, can only be as predictive as the accuracy of the dose reporting itself. Thus, reporting of the actually delivered dose over the whole treatment course, rather than an estimate derived from a single calculation performed before the course commences, will become increasingly important. Finally, with the increasing investigation of **new biologies** with protons such as grid and FLASH irradiations (Mazal et al 2020), new and hitherto ignored delivery parameters, such as estimates of delivered dose rates and/or biological models estimating their effects, will need to be incorporated into the planning process (see article on "Delivery Technology").

Advances in technology to meet challenges

Exploiting and taming flexibility: Much still needs to be done to fully exploit flexibility in PBS proton treatments. Obvious examples are developments in robust and LET based optimisation, both of which are covered in detail in other sections of this article (see also roadmap articles on "Robust Optimization" and "RBE Clinical Impact"). However, an as yet, not fully exploited potential is the optimization of pencil beam placement within the field. For instance, as has been shown by Meier et al (2017), dose confirmation can be substantially enhanced using more flexible spot placement techniques such as contour scanning, where pencil beams are first placed on exactly the surface contour at any given depth, thus contracting the high dose contour closer to that of the target volume. Alternatively, spectacular reductions in the number of pencil beams per field, whilst preserving or even improving dose conformation, have been demonstrated through the inclusion of 'spot reduction algorithms' into the optimization process (van de Water et al 2013). Such approaches however can be considered to be just surrogates of the true 'holy grail' of PBS planning - the ability to flexibly and comprehensively include spot placement, spot size and delivery dynamics (e.g., energy switching layer and scanning times) directly into the optimization process, and much interesting work remains to be done in this direction.

There is similar potential in the optimization of field directions and plan geometries. By plan geometries here, we mean the not necessarily trivial combination and overlapping of different fields during the planning process. For instance, one of the major advantages of the stopping characteristics of protons is the ability to significantly spare normal tissue through the use of 'split fields', whereby different fields

cover different portions of the full target volume or volumes (see e.g. Lomax 1999, Widesott et al 2011)). In the future, such approaches will be included directly in a comprehensive optimization approach including both field directions and (if necessary) target splitting. Although it is clear that the degrees of freedom open to the optimizer for such an approach are huge, such developments will be pursued in parallel with the development of ultra-fast dose calculation engines (Matter et al 2019) which can efficiently and quickly search the huge solution space that is opened by such techniques. Indeed, such developments will also open the door to a more automated, and therefore consistent, approach to the treatment planning of PBS proton therapy, a solution that will also be augmented by developments in machine learning and knowledge based approaches to the treatment planning problem. Indeed, such developments may well be decisive in 'taming' degeneracy in treatment planning of PBS proton therapy, introducing planning consistency, thus enabling a more fair and effective method for selecting patients for proton therapy when working with (e.g.) model based approaches (see e.g Arts et al 2017 or Bijman et al 2017). As such, the current downside of the flexibility of PBS proton therapy - potential inconsistencies in plan quality between centers and plans - will be drastically reduced.

Mitigating anatomical change: The mitigation of anatomical changes in proton therapy is particularly challenging for many sites, simply because the nature of those changes are difficult to predict. However, in some sites, anatomically robust optimization has been shown to be possible where such changes are localized and can be well modeled (Cubillos-Mesías et al 2018, van de Water et al 2018, Yang et al 2020), and more developments are foreseen in this direction (see article on "Robust Optimization"). In particular, the use of morphological changes to the planning CT to model potential weight changes or physiological deformations (Kainz et al 2019) may have promise as future inputs to anatomical robust optimization approaches. On the other hand, and as described in detail in another contribution to this article (see also roadmap article on "Adaptive Therapy" and Albertini et al 2019), the management of anatomical change will move more and more into the direction of rapid, even daily adaption of the treatment to 'anatomy-of-the-day' volumetric image taken immediately before the delivery of each fraction.

Such an approach poses a number of challenges, and opportunities, to the treatment planning process, such as the delineation of target and OAR's on the daily volumetric data set, ultra-fast plan adaption or re-optimization, and efficient and automated plan verification tools. For target and OAR definition on the daily image set, either accurate and reliable deformable warping of the original volumes between the original plan and the daily patient geometry, or fully automatic delineation algorithms will need to be developed. Indeed, many advances have been made recently in the latter (Giraud et al 2019), and it would seem that this is the direction with the most promise in the future. Even with this approach however, additional developments in treatment planning systems will need to be made in order to provide the clinician with feedback on the 'plausibility' of the automatically generated or deformed contours before applying the adapted plan, and such tools must be efficient enough to not substantially delay the adaptive process.

Rapid plan adaption, such that a completely new or adapted plan can be calculated and validated in just a few minutes, will require developments in ultra-fast dose calculations and optimization, or alternatively, methods to determine and correct just those pencil beams of the original plan most affected by the changes (Botas et al 2018). Indeed, for adaptive plan optimization, different approaches can be foreseen. First, dose-restoration techniques may be used, whereby the plan-of-the-day is automatically adjusted to be as close to the original plan as possible, substantially mitigating the amount of plan specific validation and verification necessary (Bernatowicz et al 2018). Alternatively, tools for a full, 'from scratch' re-optimization, potentially involving beam angle adjustments as well, will be developed, which can additionally take into account any preferential features of the anatomy of the day, helping to possibly

improve the quality of the treatment in relation to the original plan (Nenoff et al 2019). Similarly, and as proposed by Yan in his seminal paper on adapted therapy (Yan et al 1997) feedback loops could be incorporated into the adaptive process, whereby the accumulated doses from previous fractions are used as an input to the daily optimization process. This way, the 'plan-of-the-day' could also adapt on any deviations of the accumulated dose away from the reference plan (for instance as a result of interrupted previous treatments) or even capitalize on advantageous anatomical changes taking place over the course of the treatment (see e.g. Matter et al 2020).

Finally, alternative, treatment planning based methods for plan validation will need to be developed, such as fast, fully independent dose calculations which can reconstruct the dose from (e.g.) machine control data before the plan-of-the-day is delivered (Matter et al 2019). Such developments will require an ever closer cooperation between the delivery machine and treatment planning system manufacturers (see article on "4D planning and Delivery").

Clinically relevant dose reporting: As we move towards treatment adaption to multiple imaging data sets of the patient, the problem of recording what dose was actually delivered to the patient at what point becomes increasingly challenging. However, such data is essential for the development of accurate biological models for outcome prediction (see article on "Outcome Modeling"). Although tools for registering two or more data sets together in 3 dimensions are mature, particularly for the deformable problem, the solution is notoriously degenerate, with different systems providing quite different solutions (Nie et al 2016; Nenoff et al 2020). As such, future developments in dose accumulation, together with associated 'uncertainty' maps indicating those regions where the accumulated dose can be trusted to a greater or lesser extent, will need to be developed (Heinrich et al 2016). This would be analogous to the calculation and presentation of dose uncertainty as part of robust plan analysis methods already available in most commercial treatment planning systems. Indeed, uncertainties of all types are an integral part of the radio- and proton therapy process, and as such can provide valuable information to the planning physician or also, eventually, as an additional parameter to include into outcome analysis and biological modeling. As such, dose reporting should also include standardized ways of reporting spatially varying uncertainties in calculated and delivered dose, as well as biological paramaters such as LET, both of which are important for proton therapy if we wish eventually to understand their clinical relevance.

Planning for new biologies: Finally, it is perhaps too early to speculate on what changes to treatment planning systems will be required to plan for FLASH or Grid irradiations. For both, current dose calculation engines will likely be accurate enough to provide accurate estimates of the 3-dimensionally varying dose delivered to the patient. But given that the response of tissue to both techniques will be quite different to that of conventional therapy, even before we develop the appropriate biological models, new metrics for quantifying such plans will need to be developed. For FLASH, this will likely be in the direction of spatially varying spectrums of dose-rates (van de Water et al 2019, van Marlen et al 2020) which would, similarly to the validation of adaptive plans discussed above, require a close cooperation between treatment machine and therapy planning manufacturers. Based on these, and as our knowledge of the clinical FLASH effect becomes deeper, there will be the need to start to incorporate a biological 'FLASH' effect as a function of dose rate, in an analogous way to RBE and its relationship with LET. Only through the development of such tools can we hope to be able to effectively plan FLASH treatments. For grid-based treatments, other tools may be necessary. As the sparing of normal tissue will be dependent on the peak-to-valley dose ratio and its spatial separation, treatment planning systems may need to provide tools for quantifying and optimizing this in an analogous way to dose volume histograms, or provide metrics for quantifying the heterogeneity (or 'gridness') of the dose distribution in normal tissues and the tumor.

Concluding remarks

The relative immaturity of PBS proton therapy, together with the need to mitigate (and record) uncertainty, leads naturally to many challenging and interesting developments still to be done in the treatment planning of proton therapy. When also considering the exciting areas of FLASH and grid therapy, which are themselves challenging our conventional thinking of biology and what is a 'good' treatment plan, developments in treatment planning are anything but dead. Indeed, it is an area ripe to be exploited and where much still needs to be done.

Development of robust planning

Jan Unkelbach

Proton therapy practitioners have long been aware of dose uncertainties in proton therapy and have developed strategies to account for uncertainty in treatment planning (Paganetti, 2011) (see article on "Uncertainties"). In the era of passive scattering based proton therapy, this included increasing range and modulation of spread-out Bragg peaks, widening apertures, and compensator smearing. For complex geometries requiring patch fields, multiple patch field combinations were used to mitigate the effect of misaligned fields. In the era of pencil beam scanning, treatment planning became based on mathematical optimization techniques similar to intensity-modulated radiotherapy (IMRT). The similarity to IMRT made it natural to apply the planning target volume (PTV) concept to proton therapy planning. However, it was soon realized that the PTV concept has limitations in proton therapy. The fundamental assumption behind the PTV concept, that the CTV receives the prescribed dose as long as it moves within the PTV, is not generally valid for proton therapy. Range and setup errors may lead to misalignment of dose contributions of different beams, misalignment of tissue heterogeneities in the entrance region may degrade dose distributions, and thus PTV coverage does not guarantee CTV coverage even if PTV margins are large. A commonly used heuristic to improve robustness is referred to as single field uniform dose (SFUD), which mitigates dose degradation due to misalignment of dose contributions from different beams. However, for complex shaped target volumes, SFUD compromises treatment plan quality compared to intensity-modulated proton therapy (IMPT). In addition, dose degradation due to misalignment of tissue heterogeneities is not addressed. Robust optimization methods were developed to address these limitations and refer to mathematical optimization techniques that directly incorporate uncertainty into the formulation of the IMPT optimization problem.

Status of robust optimization

Robust planning can be divided into robustness evaluation (i.e. assessing the sensitivity of a given treatment plan to errors) and robust optimization (i.e. the process of obtaining a treatment plan that is robust against errors). In photon therapy, robustness is indirectly assessed by evaluating the dose distribution in the PTV. As it has been recognized that coverage of the PTV does not guarantee coverage of the CTV in proton therapy, the main commercial treatment planning systems (TPS) now allow for evaluating the dose distribution for individual error scenarios. In addition, various measures to assess dose uncertainty such as confidence intervals around DVH lines have been suggested but only a subset of those is available for practitioners. In addition, the main TPS have an implementation of robust optimization. (see article on "Treatment Planning")

In IMPT optimization, an objective function f, which is a function of the dose distribution d, is minimized with respect to pencil beam intensities x. Under uncertainty, given pencil beam intensities x may lead to different dose distributions d_s for error scenario s. Practically, the goal is to obtain a treatment plan that is of high quality for all or most anticipated errors. There have been three approaches

to translate this practical goal into mathematical terms that led to implementations in the main commercial TPS.

1. Stochastic optimization, also referred to as probabilistic treatment planning, assigns probabilities p_s to the error scenarios and optimizes the expected plan quality (Unkelbach *et al.*, 2009). This approach is implemented in the Pinnacle planning system (Philips Healthcare).

$$\underset{x}{\text{minimize}} \sum_s p_s f\big(d_s(x)\big)$$

2. Minimax optimization (Fredriksson *et al.*, 2011), also referred to as composed worst case optimization, determines the pencil beam intensities such that the dose distribution is as good as possible for the worst error scenario considered. Minimax optimization is implemented in Raystation (Raysearch Laboratories).

$$\underset{x}{\text{minimize}} \Big[\max_s \; f\big(d_s(x)\big) \Big]$$

3. Optimization of the voxel-wise worst case dose distribution (Pflugfelder *et al.*, 2008) can be considered a variation of minimax optimization. Here, the minimum doses in target voxels and the maximum doses in normal tissue voxels are considered. The resulting voxel-wise worst-case dose distribution is used for evaluating the objective function. The approach is implemented in Eclipse (Varian).

Other methods, such as minimax stochastic optimization (Fredriksson, 2012), which interpolates between optimizing average and worst-case plan quality, have been proposed, but are currently not available for practical use in commercial systems. An extensive review is provided elsewhere (Unkelbach *et al.*, 2018). For illustrations of robust optimization and comparisons to PTV-based plans, we refer to the original publications. The variety of methods implemented in different commercial systems suggests that there is no single robust planning method that is found to be generally superior. It has been shown that individual methods have disadvantages in specific situations, however, in most cases different robust planning yield very similar results. Publications comparing methods are scarce. Regarding the types of uncertainty, most of robust IMPT planning research has focused on systematic range and setup errors. In the research literature, extensions to other uncertainties such as respiratory motion have been considered but are only partially supported in some TPS. (see articles on "Treatment Planning" and "4D Planning and Delivery")

Current limitations and future challenges

Establishing consensus for robustness evaluation: In photon therapy, plan robustness is indirectly assessed by evaluating coverage of the PTV. Although this may have limitations also in photon therapy, it allows for establishing consensus that is needed, for example, in the design and reporting of multi-institutional trials. Concepts for robustness evaluation for protons have been proposed (Korevaar et al., 2019). However, there is no general consensus yet on how to assess and report the robustness of proton plans, which should be addressed in future working groups.

Optimization based on relevant plan quality indicators: Most robust optimization methods currently available were developed by applying known methods from the optimization literature such as minimax or stochastic optimization to the IMPT planning problem. Thereby, common objective functions such as quadratic penalty functions are robustified. However, the expectation or worst-case values of quadratic

penalty functions are only surrogates for plan quality. In practice, DVH based criteria are considered, for example, a treatment plan may be acceptable if 95% of the target volume receives the prescription dose in 90% of the scenarios. Future work may aim at facilitating robust treatment plan optimization using relevant plan quality indicators as objective and constraint functions.

Beyond systematic range and setup errors: Current research and support in commercial systems has focused on systematic range and setup errors. Typically range errors are modeled by up- or down-scaling of Hounsfield units of the planning CT. Thereby, it is assumed that range errors affect all pencil beams in the same way, that is, all pencil beams overshoot or undershoot synchronously. Setup errors are modeled as rigid shifts of the patient. These models of uncertainty are simple to implement, however, the real source of uncertainty is more complex. Today, range and setup errors are used as surrogates for other uncertainties such as internal organ motion (see articles on "Adaptive Therapy" and "4D Planning and Delivery"). Complex geometric variation is difficult to model based on a single planning CT scan prior to treatment. Nevertheless, future work may consider the development of site-specific uncertainty models for evaluation and optimization that reflect the characteristic uncertainty of specific treatment sites (see article on "Treatment Planning").

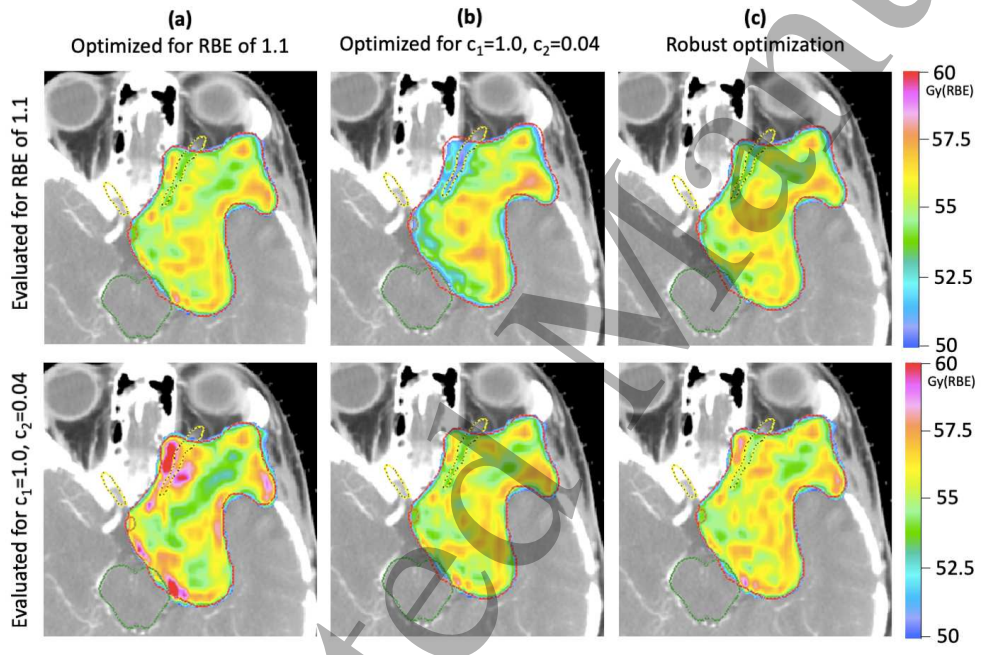

Figure 1: Illustration of stochastic programming applied to parameter uncertainty in RBE models. A simple model for RBE-weighted dose, $RBE \cdot d = (c_1 + c_2\, LET) \cdot d$, is considered. RBE uncertainty is modeled via 3 scenarios: 1) a constant RBE of 1.1 ($c_1^s = 1.1, c_2^s = 0$), 2) a variable RBE with ($c_1^s = 1.0, c_2^s = 0.04$ µm/keV). This corresponds to the assumption that the RBE of a proton pencil beam is 1.0-1.1 in the entrance region, 1.2-1.3 near the Bragg peak, and 1.5-1.6 in the falloff region. 3) an intermediate scenario ($c_1^s = 1.05, c_2^s = 0.02$ µm/keV). An RBE-weighted dose of 54 Gy(RBE) is prescribed to the target volume, and 57 Gy(RBE) was allowed in parts not overlapping OARs. Figure 1a (bottom row) demonstrates the problems with conventional planning based on a RBE of 1.1. When evaluated for variable RBE, hot spots >60 Gy(RBE) in OARs overlaying the target can be observed, resulting from high LET. Figure 1b (top row) shows issues with IMPT optimization based on a fixed RBE model. The method leads to lower physical doses in parts of the target, potentially leading to underdosage (<50 Gy(RBE)) if the LET effect on RBE is overestimated by the model. Figure 1c shows that robust optimization incorporating RBE uncertainty yields adequate target dose distributions in both situations.

Computationally efficient methods: Robust optimization remains a computationally demanding task, depending on the number of scenarios considered, and may lead to long computation times. Several approaches to address computation time are being investigated and may be brought to an application in the future. Perko et al. (2016) developed a methodology allowing fast robustness evaluation of treatment plans. In their approach, the dose distribution is evaluated for a limited number of error scenarios; subsequently, these dose distributions are fit with a set of polynomial basis functions. Thereby, a model of the dose distribution as a continuous function of the error is obtained, which can be used for further robustness evaluation at almost no additional computation time. Bangert et al. (2013) pursue an alternative approach to probabilistic treatment plan evaluation and optimization going beyond a discrete set of error scenarios. The underlying idea is to consider Gaussian range and setup errors in combination with a Gaussian parameterization of pencil beam dose distributions. In that situation, one can exploit the fact that the convolution of Gaussian functions can be done analytically. This allows, for example, efficient evaluation of the expectation and variance of the dose distribution.

Applications to biological uncertainties: So far, robust optimization was mostly investigated for geometrical uncertainty. In parallel, treatment planning methods to account for variable relative biological effectiveness (RBE) have been researched. This includes treatment plan optimization based on RBE-weighted dose (Wilkens and Oelfke, 2005), but also methods to incorporate linear energy transfer (LET) into IMPT optimization (see article on "Relative biological effectiveness") . One of the challenges in this domain is the uncertainty in RBE. Some LET-based methods can be understood as heuristics to make IMPT plans robust against uncertainties in RBE. However, an alternative is to apply robust optimization techniques to account for uncertainty in the parameters of an RBE model (Unkelbach and Paganetti, 2018). This is illustrated in Figure 1 for an atypical meningioma patient in whom the target volume (red) overlays the brainstem (green) and the optic nerves (yellow).

Concluding remarks

Robust planning support is implemented in the main commercial TPS for proton therapy. Thereby, robust optimization has matured from a research topic to a technique that is routinely used for treatment planning in clinical practice. Future work in this domain may aim at establishing consensus for robustness evaluation and reporting, facilitate robust optimization based on such agreed-upon robust plan quality indicators, develop site specific uncertainty models beyond systematic range and setup errors, and reduce computation times for robust planning.

Adaptive Therapy to Account for Daily Anatomy and Range Variations

Lei Dong and BK. Kevin Teo

Status

It is well recognized that the proton therapy dose distributions are more sensitive to patient's anatomic changes (Engelsman et al., 2013; Muller et al., 2015; Hoffmann et al., 2017) (see article on "Uncertainties") compared to photon therapy. Adaptive radiation therapy (ART) is becoming a critical tool for some treatment sites, such as head & neck (Muller et al., 2015; Gora et al., 2015) and lung cancers (Gomez and Chang, 2011; Hoffmann et al., 2017) which are known to have large anatomical changes during treatment course due to treatment effects, such as tumor shrinkage, weight loss, pleural effusion, atelectasis etc. It is a common practice to repeat the simulation CT to evaluate patient's anatomical changes and re-calculate the original proton plan on the updated CT or 4DCT images to assess target coverage and normal tissue sparing. When necessary, offline ART is performed to improve dose conformality.

Unlike photon therapy, there are additional factors that can trigger a proton plan adaptation. For example, changes outside of the target volume, which include but are not limited to radiological pathlength variations due to patient's anatomy, changes of couch top or immobilization devices relative to the simulation position, heterogeneity changes etc. While robustness optimization is a planning strategy to manage potential rigid setup errors and expected range variations, ART is a personalized approach to deal with actual changes during treatment.

Although offline ART is becoming a common practice in proton therapy, it is still a time- and resource-consuming process. The primary steps in ART include re-simulation, re-contouring, original plan evaluation, and re-plan (ART) if necessary, with the associated quality assurance procedures for new plans. While some of these steps can be assisted by auto-segmentation or auto-planning tools, human intervention is still required because these tools are not perfect and there are many required steps (such as manual importing images, physician's availability and adequate time to review plans etc.), even if computational resources are not a constraint. There are no clear guidelines on how often patients should be evaluated for anatomical changes or well-defined criteria that should be used to trigger ART. Nevertheless, in-room volumetric imaging using CBCT or CT-on-rails has become a standard configuration for modern proton therapy (Landry and Hua, 2018); qualitative or quantitative evaluations of patient's anatomy have become more convenient. This trend of using online volumetric imaging should increase the utilization of ART for proton therapy in the near future.

Current and future challenges

ART is an interventional process that requires adequate feedback (online/offline imaging), decision support (criteria for replanning) and corrective strategies. The general process and selected contents specific to proton therapy are summarized in Figure 2. It is important to realize that there are many factors that can impact conformal dose delivery. Proton ART may be limited by the correction strategies (offline, online or real-time) or imaging techniques to detect specific changes in patients. An offline ART approach can correct systematic or slow changes in anatomy, but may be limited in adapting daily physiological variations in setup position.

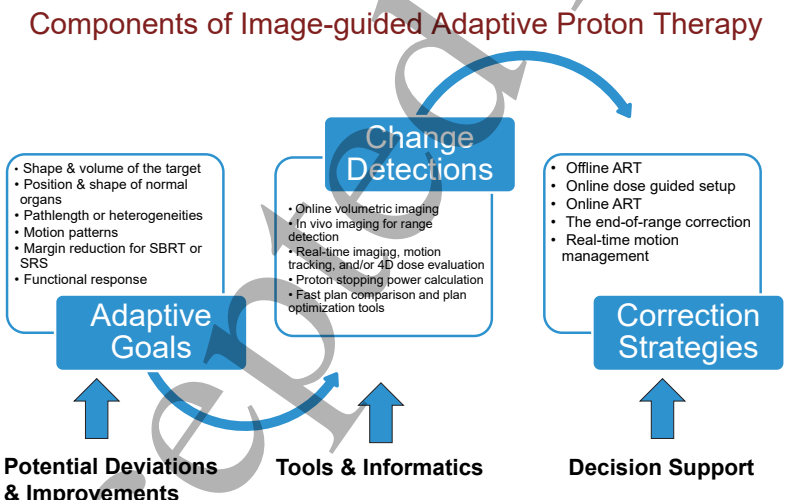

Figure 2: Adaptive Proton Therapy is an interventional process that requires imaging and algorithms to detect changes and identify improvements, and then a subsequent corrective strategy.

Although the offline ART seems to be a practical approach, the process itself can benefit from streamlining and automation in many steps: CT image artifact removal, density overrides for couch/immobilization structures, auto-contouring of targets and organ at risks (OARs), faster dose calculation and plan comparison tools. If a new ART plan is requested, a faster treatment optimization and efficient QA may be needed. Sometimes, transferring the approved plan to vendor's treatment console and updating treatment calendar for the new plan would require additional manual intervention. Because this is a time-consuming manual process, few proton therapy patients are currently benefiting

enough from offline ART. For those centers that do, imaging frequency, contouring, and quality of ART plan may be suboptimal due to time constraint and resource limitations. Therefore, the current biggest needs are the development of automation tools that can support proton ART workflow.

Figure 3: Scoring sheet for common online/offline correction strategies and their corresponding uncertainties. WET: Water-Equivalent-Thickness; OAR: Organ-At-Risk.

Variation Factors	Offline ART	Online ART	Online Range Adapted RT
Systematic WET/Target	✓	✓	✓
Daily WET/Target	X	✓	✓
Proton Range Calculation	X	X	✓
Distal OAR Sparing	X	?	✓
Intra-fractional Motion	X	?	?

Recently, there has been enormous progress in developing online adaptive photon therapy (Wang et al., 2017). Some of these tasks are identical for proton ART (for example, auto-segmentation on CT or CBCT images) while others share a similar approach. For example, the use of GPU for fast dose calculation or plan optimization (Matter et al., 2019), and quality assurance (Wang et al., 2017), which are critical for online ART. Near real-time dose restoration to account for daily tissue density variations using an on-line range adaptation of individual spot energies (Zhang et al., 2011) with readjustment of some spot weights (Jagt et al., 2017) is one approach that permit fast plan re-generation for online ART (see section on Treatment planning for pencil beam scanning proton therapy). A summary of proton ART strategies and correction goals are listed in Figure 3.

A more difficult problem is to convert Hounsfield Unit (HU) from online CBCT images into accurate proton stopping power ratios that are required for dose calculation. Some investigators used a virtual CT approach, which matches CBCT HU to the corresponding simulation CT images using a deformable image registration method (Veiga et al., 2016) and others used scatter correction to create a high quality CBCT similar to the conventional CT scanner (Nomura et al., 2019). Recently, machine learning based approaches seem promising in directly converting CT numbers into proton stopping power (Nomura et al., 2019; Kurz et al., 2019). Each of these approaches creates additional uncertainties, which should be factored in the implementation of ART.

An ideal approach for online ART might involve the use of in vivo imaging for proton range correction (see article on "In vivo range verification"). Because range uncertainties are the primary reason for plan adaptation and also responsible for suboptimal quality in the original plan due to uncertainties in proton stopping power conversion (Yang et al., 2012), an online range-adapted proton therapy approach would be appealing if the proton range can be accurately detected and corrected just prior to treatment delivery. In vivo range detection is still under intense research, and investigated approaches include but are not limited to (1) in-room proton CT (Sadrozinski et al., 2016); (2) prompt gamma detection (Hueso-Gonzalez et al., 2018; Xie et al., 2017); (3) proton radiography (Deffet et al., 2017); (4) proton-acoustic wave detection (Patch et al., 2019) etc. If successful, one additional benefit is to use the sharp falloff of the Bragg peak to spare distal OAR, which has not been fully utilized in conventional proton therapy due to range uncertainties (Hoesl et al., 2016). Data from in vivo imaging can be used in two ways. First, if systematic range shifts due to inaccuracies in proton stopping power are detected, the plan may be adapted to reduce these shifts for subsequent fractions. Second, in vivo range verification offers a real-time quality assurance of the online ART plan when traditional measurement-based QA with phantom is not feasible.

Other challenges are related to the rapid variation of proton range due to breathing motion and beam interplay effects (Mori et al., 2018). For treatment sites that experience a large organ motion, 4D cumulative dose calculation may be needed to evaluate plan robustness for both inter- and intra-fractional changes (Li et al., 2012) (see article on "4D planning and delivery"). ART planning may need to incorporate plan robustness to minimize motion effects (Liu et al., 2016). ART planning can also be used

to compensate patient specific motion patterns (Li et al., 2015).

Concluding remarks

Due to many technical and practical issues, proton ART is in its infancy. The biggest challenge now is to develop reliable tools (such as data processing, informatics, plan review, decision support, auto-planning, quality assurance etc.) to make the entire process more efficient and practical. Currently, there is no consensus on what anatomic or dosimetric change would be required to trigger ART that will optimize the treatment. However, the dosimetric benefit of proton ART is well accepted by the proton therapy community. Parallel to the development in photon therapy, online proton ART is the upcoming strategy that can bring perhaps the biggest dosimetric benefit to proton therapy patients (Albertini et al., 2019). Ultimately, the success of ART has to be associated with improved clinical outcome. For example, Yang et al. demonstrated that ART improved 5-year overall survival for a subgroup of lung cancer patients with poor initial conditions (i.e., large tumors), presumably due to improved dose conformality (Yang et al., 2019), although more studies are needed.

In vivo range verification

Katia Parodi

Status

Already back in the early pioneering phase of proton therapy, Bennett et al postulated the possibility of controlling the surface of maximum beam penetration, which relates to the ability of depositing the dose maximum (Bragg peak) in the tumor while sparing the normal tissue behind, by visualizing the β^+-activity generated through nuclear interactions of protons in tissue (Bennett et al 1978). Their seminal work not only showed that a prototype on-line positron emission planar camera was able to visualize in a live pig the pattern of proton-induced activation, which was mostly ascribed to ^{11}C, ^{15}O and ^{13}N fragmented tissue nuclei, but also foresaw the use of such positron emission measurements for reconstruction of the delivered dose. Moreover, they emphasized the importance of on-line detection for analysis of the biological transport of irradiation-induced radionuclides, which is relevant to the localization and reconstruction of the delivered dose, and even suggested to provide useful information on regional blood flow. Nevertheless, due to the technological challenges for development and integration of dedicated positron-emission-tomography (PET) scanners in the treatment delivery, most of the following investigations in phantoms and first clinical pilot studies were pursued after treatment using nuclear medicine PET and PET/CT (computed tomography) full-ring diagnostic scanners (Parodi and Polf 2018). Such in-room and offline volumetric imaging approaches suffer from issues of physical and biological decay in the time elapsed between irradiation and imaging, along with possible changes of the patient position, all degrading the correspondence between the physically produced and the image reconstructed activity (Parodi and Polf 2018, Shakirin et al 2011). Although most of these issues can be overcome with the ongoing re-implementation of on-line detection approaches (Parodi and Polf 2018, Shakirin et al 2011, Ferrero et al 2018), the PET signal can be considered intrinsically delayed with respect to the beam delivery according to the half-life of ~2-20 min of the most abundant positron emitting reaction products. Hence, in 2003 Stichelbaut and Jongen raised the question why not verifying the proton beam position in the patient by the detection of prompt gamma (PG) rays emitted in the very fast (sub-ns scale) de-excitation processes after nuclear interaction (Krimmer et al 2018). However, due to the high energies of such PG emissions in the MeV range, it took several years of computational simulations and detector development (Krimmer et al 2018) to arrive at first viable prototypes of collimated cameras (Xie et al 2017, Hueso-González et al 2018), only able to capture a one- or two-dimensional projection of the distal PG signal generated from each individual pencil beam delivered to

the patient. Remaining challenges entail further improvements of detector technologies along with interpretation and utilization of these (or even other) secondary emissions, typically in comparison to an expectation, to devise new strategies for ideally real-time beam range verification and quantification of the actual dose delivery for prompt treatment adaptation. These efforts will also largely benefit from as well as complement the ongoing developments in in-room volumetric and even time-resolved anatomical image guidance (see article on "Image Guidance").

Current and future challenges

State-of-the-art on-line PET and PG detectors are just entering the phase of clinical evaluation with the most modern form of scanned proton beam delivery. At the combined proton and carbon ion therapy facility of CNAO (Centro Nazionale di Terapia Oncologica) in Italy, a dual-head PET scanner based on modern scintillation crystals (Lutetium fine silicate) and photosensors (multi-pixel photon counters) is used to dynamically (every ≈10 s) reconstruct the irradiation induced activity during treatment, with very promising initial clinical results (figure 4) (Ferrero et al 2018). Here, a major challenge is the still outstanding ability of using the events measured during the actual beam delivery (spills), due to remaining background from prompt radiation (including PG), despite a dedicated data acquisition system aiming to suppress it. Moreover, reconstruction and visualization of the data acquired during the interrupts (pauses) of the synchrotron-based beam delivery still requires 6 seconds, impeding a truly real-time imaging. It seems possible to achieve sub-mm reproducibility of distal range measurements in different treatment days, but accuracy between PET measurements and predictions remains at the still unsatisfactory level of a few millimeters (figure 4) (Fiorina et al 2018), thus demanding further improvements of the underlying modeling. The ongoing clinical evaluation and further methodological improvements will thus enable assessing whether the desired range localization accuracy of less than 1-2 mm can be achieved, going beyond the reported accuracy of PET-based verification in the order of 2-5 mm for the earlier less optimal clinical implementations (Parodi and Polf 2018; Parodi 2018).

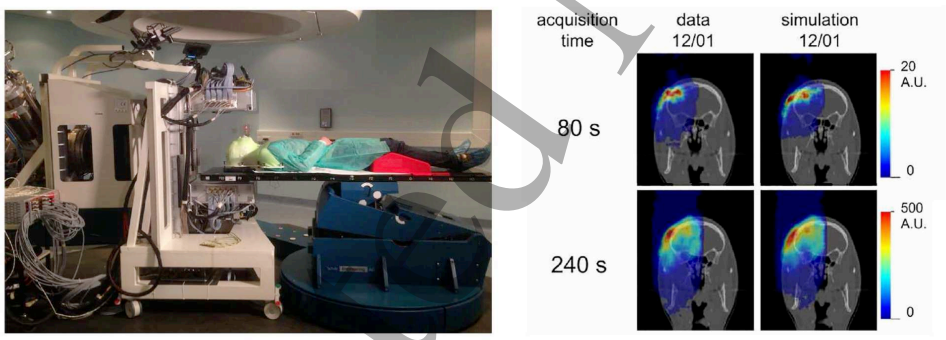

Figure 4: Example of the dedicated in-beam PET scanner in treatment position at CNAO (a) and the dynamically reconstructed PET activation data in comparison to the simulated predictions (b) in two different time windows during proton beam delivery. The PET images (color wash) are superimposed onto the planning X-ray CT (grey scale). Adapted from (Fiorina et al 2018), with permission.

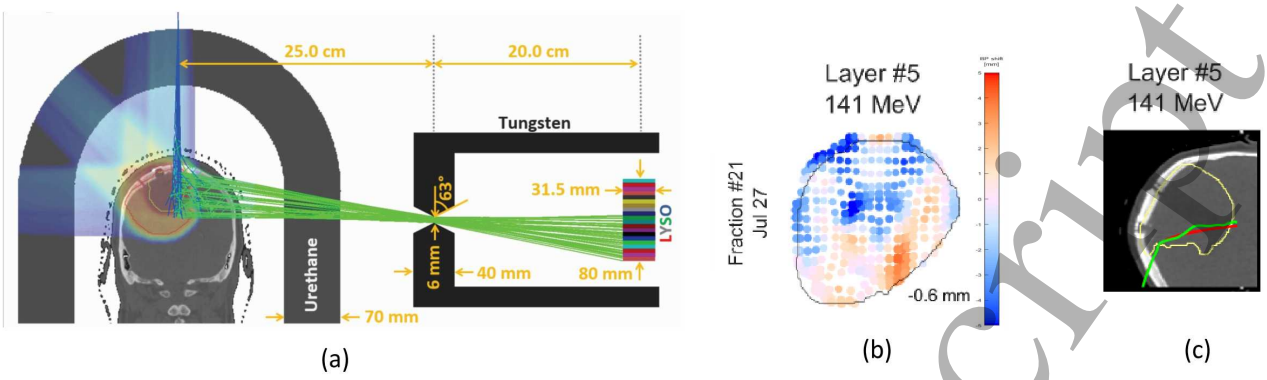

Figure 5 (a) Schematic of the knife-edge slit camera, as deployed in the first clinical study of (Xie et al 2017), projecting the PG signal (green) from the proton beam (blue) onto the position sensitive scintillators beyond the collimator. The corresponding analysis results in the spot-by-spot (with aggregation) range difference comparison in beam-eye-view (b) as well as PG-based estimation of the measured (green) and predicted (red) Bragg peak depth overlaid with the planning CT (c) for a given energy layer and treatment fraction. Adapted from (Xie et al 2017, with permission from Elsevier).

For PG, two prototypes of a single slit camera, consisting of a knife-edge collimator and position sensitive Lutetium-yttrium oxyothosilicate scintillators readout by silicon photomultipliers (Krimmer et al 2018, Xie et al 2017), are being investigated for their ability of spot-by-spot proton range recovery at University of Pennsylvania (figure 5) and University Proton Therapy Dresden. The initial clinical evaluation showed the feasibility of achieving precision (defined as standard deviation of random simulated shifts) within 2 mm when aggregating the signal from nearby pencil beams for sufficient ($\geq$ 1.2 10^8 protons) counting statistics. However, the clinical findings of average (aggregated over all spots in 9 energy layers) range shifts from -0.8 mm to 1.7 mm between measurement and expectation were mostly limited by the mechanical accuracy of the trolley positioning system, for which improvements are currently ongoing. Still, the design of this detection system can only provide one-dimensional profiles of coarse spatial resolution, challenging the performance in the presence of considerable tissue heterogeneities that distort the distal dose surface, or large tumor sizes that require a wide dynamic range of the camera field-of-view coverage. More recently, another collimated system featuring eight $LaBr_3$ scintillators behind a tungsten collimator, mounted on a rotating frame, has been thoroughly characterized experimentally prior to its clinical deployment (figure 6) (Hueso-González et al 2018). The detection system has been optimized for energy and time resolution to enable spectroscopic analysis of the gamma emissions characteristics of each specific tissue nuclei and for optimal suppression of radiation background outside the microscopically bunched beam extraction from the cyclotron. By comparing the measured signal with a sophisticated prediction model taking into account experimental data of PG emissions for different nuclear reaction channels as well as possible range error scenarios, the system can provide spot-by-spot maps of range difference (between measurement and prediction) and percentage elemental composition of carbon and oxygen (figure 6). Investigations in phantoms suggested the feasibility to retrieve the proton beam range with a mean statistical precision of 1.1 mm at a 95% confidence level and a mean systematic deviation of 0.5 mm (Hueso-González et al 2018). Hence, this level of accuracy, if confirmed in the ongoing first clinical evaluation, would be well below the one so far reported for PET-based range verification. However, also this system requires aggregation of neighboring spots to increase the signal statistics, thus challenging the achievable spatial resolution and range resolving power in the presence of pronounced tissue heterogeneities. Moreover, none of these on-line PET and PG systems integrates imaging modalities able to provide complementary information on the tissue anatomy, for co-registration with the retrieved information of the distal beam penetration depth

as well as updated patient model for attenuation (and scatter) correction.

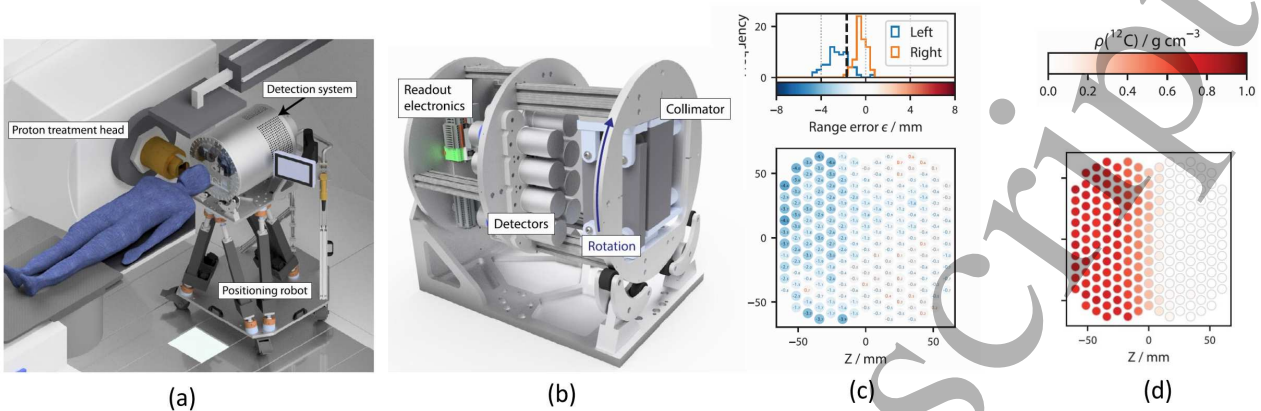

Figure 6: Schematic of the spectroscopic system of (Hueso-González et al 2018) integrated in the proton beam gantry for a representative treatment position (a), along with the details of the energy- and time-resolved detector components beyond the collimator (b). The results enable quantifying the range difference from a prediction model for each applied spot (c) along with carbon (d) and oxygen concentrations, in this example obtained when inserting a slab phantom on the left of the beam path in water (with spot aggregation). Adapted from (Hueso-González et al 2018).

Advances in science and technology to meet challenges

Ongoing research in the medical imaging community towards detectors of ultra-fast timing resolution in the order of 10 ps, along with steady progress in real-time data acquisition and processing, will certainly benefit the above described detector designs, ideally enabling real-time imaging as well as improved background suppression and image quality (Lecoq et al, 2020). For PET-based range verification, additional efforts are ongoing to exploit the signal from millisecond short-lived positron emitters (e.g., ^{12}N) to enable quasi real-time visualization of the dynamic beam delivery (Buitenhuis et al 2017), although likely at the expense of degraded spatial resolution from the typically long positron range. For PG imaging, efforts are ongoing to increase the dimensionality of the reconstructed distribution and to remove the massive collimator for enhanced detection efficiency. To this end, several prototype designs of Compton cameras have been proposed based on different detector technologies (solid state, scintillation, and thereof combination), along with alternative approaches exploiting only the arrival time of the photons or their conversion into secondary electrons (Krimmer et al 2018). Exploitation of the Compton kinematics also opens the perspective of new unconventional designs of hybrid detection systems able to reconstruct signals related to standard PET and PG emissions, as well as triple coincidences originating from special isotopes (e.g., ^{10}C, ^{14}O) that emit an additional third photon in connection with their radioactive decay (Lang et al 2014). Besides utilization of complementary photon emissions (e.g., PG during beam-on and PET during beam delivery pauses or after irradiation), triple gamma imaging offers the intriguing potential of visualizing the underlying activity with only a few detected events, thereby also opening the perspective of an almost real-time imaging, at the expense of the lower probability of such events (Lang et al 2014). This ability could also be exploited to combine in-vivo range verification with additional nuclear tracer imaging for localization of the tumour or specific biomarkers to provide image-guidance during treatment, ideally also time-resolved for moving targets. Regardless of the final technological implementation and imaging approach, information on the in-vivo range will likely still rely on a comparison between the measured and predicted signal. To this end, considerable progress is expected from the emerging ability of embedding fast predictions of PET and

PG signals in treatment planning engines (Pinto et al 2020), which also enables accounting for the counting statistics required for reliable monitoring in the treatment planning approach (Tian et al 2018, 2020). Improved accuracy of these computational models will also largely benefit from the ongoing efforts of the scientific community to provide more accurate experimental measurements of underlying nuclear cross section data and resulting PET and PG yields in clinically relevant targets (Horst et al 2019). Moreover, advances in artificial intelligence and deep learning approaches will also support the implementation of novel and fast workflows which can provide almost real-time feedback on the dose delivery (Liu et al 2020) to devise prompt correction strategies even during patient irradiation.

Concluding remarks

The considerable ongoing progress in instrumentation and computational methods for PET and PG imaging will likely enable reliable and almost real-time (sub)millimeter accurate monitoring of the beam range in the patient in the near future, which would be a major step forward with respect to the so far attempted applications of these technologies in clinical pilot studies. Although PG can offer advantages in terms of range localization accuracy and real-time information, PET provides an intrinsically 3D imaging modality lending itself to the possible combination with tracer imaging. Imaging annihilation and single photon emissions with a single device (Yoshida et al 2020) will open new prospects for making the most of both technologies during different portions of the irradiation (e.g,. PG during beam-on and PET during beam-off) and evaluate their strengths and limitations in different anatomical sites. These nuclear-based technologies of general applicability, already finding their way into clinical translation, will likely be complemented by the less mature technologies currently under investigation for specific anatomical locations, using different kinds of secondary emissions (e.g., thermoacoustics for pulsed beams or secondary protons) or pre-treatment range probes (Parodi and Polf 2018). All these efforts in range verification will also benefit from and complement the ongoing developments for improvement of the daily patient model at the treatment place based on different flavours of X-ray, proton and magnetic resonance and, especially in the case of thermoacoustics, ideally intrinsically co-registered ultrasound imaging (see articles on “Image-guidance” and “Adaptive therapy” as well as Parodi (2018)). Together with the further development of very promising methods of dose reconstruction from the measured emissions (Masuda et al 2019), advances in the monitoring of proton treatment will provide real-time information of the beam position in the patient and ideally of the applied pencil-beam dose in the underlying updated patient anatomy, for prompt interruption of erroneous delivery or new adaptive treatment schemes. Also, changes in the detected signals over the course of fractionated therapy could be exploited to monitor processes correlated to treatment response, such as biological washout (e.g., accessible with PET imaging, as already shown in the seminal work of Bennett et al 1978) or oxygen concentration (e.g., accessible with PG spectroscopy) (Parodi and Polf 2018), as recently reported for phantom studies by (Martins et al 2020). This would thus open a new dimension of biology-driven treatment personalization, beyond the more physics-driven scope of range monitoring and dose reconstruction for truly adaptive therapy.

4D planning and delivery

Antje-Christin Knopf

Status

By now the great majority of new proton therapy (PT) centers is equipped with pencil beam scanning (PBS) solely. The high precision of PBS-PT comes as a double-edged sword, especially for moving targets. Highly conformal dose distributions have to be delivered in a robust manner to address the high sensitivity of PBS-PT to uncertainties. Over the past few years, treatments for lesions with intra-fraction

motion significantly increased in number due to the availability of robust optimization, evaluation and quality assurance tools, increasing confidence. However, the influence of uncertainties has to be further minimized to exploit the full benefit of PBS-PT for moving indications of all characteristics.

Current and future challenges

4D imaging: Inter-fractional variations of breathing pattern and patient anatomy introduce dose uncertainties in PT. Only in recent years, with the introduction of in-room computed tomography (CT) and cone-beam CT (CBCT) for patient positioning, it has become feasible to monitor these variations without relying on external surrogates (Landry and Hua 2018). However, to make more use of the daily acquired CBCTs for daily 4D dose recalculations, 4D reconstruction and 4DCBCT-based 'virtual 4DCT' generation has yet to be established and to be implemented clinically. So far, the use of 4DCBCT for adaptive PT for lung cancer has been studied in silico (Veiga et al 2016). Also, in a phantom setting the feasibility of 4DCBCT-based proton dose calculation has been demonstrated (Niepel et al 2018).

Intra-fractional variations, occurring during beam delivery, still can only be monitored by external surrogates and thus remain largely undiscovered. The broader clinical implementation of fluoroscopy during beam on might give intra-fractional insights using internal surrogates (Shirato et al 2012). Future developments towards combined MR-PT machines might enable full 4D online monitoring.

4D optimized planning: 4D optimized planning has recently become available in commercial treatment planning systems (Engwall et al 2018). Several studies have shown that the incorporation of respiratory motion, along with setup and range uncertainties, into 4D robust optimization, has the potential to improve the resilience of target and normal tissue dose distributions in PBS-PT plans in the face of the uncertainties considered (Liu et al 2016, Cummings et al 2018, Ge et al 2019). However, 4D optimized planning remains computationally expensive and time consuming, requiring further developments to make it more widely usable in clinical routine (Pepin et al 2018). Furthermore, the impact of different deformable image registration (DIR) algorithms (Ribeiro et al 2018) and the physical correctness of dose accumulation remain topics of concern for 4D optimized planning (see article on “Treatment Planning”).

4D evaluation: Papers addressing the robustness evaluation of PBS-PT plans for moving indications mainly report on the impact of setup and range errors, breathing motion and interplay individually. Only recently also studies on the combined impact of different uncertainties have become available (Inoue et al 2016, Ribeiro et al 2019). These comprehensive 4D robustness evaluation methods are essential to safely extend PBS-PT to moving indications. They allow the assessment of full PBS-PT treatment courses for moving targets, helping to define optimal clinical protocols for this group of patients.

4D delivery / motion mitigation: While in a research context all kind of sophisticated motion mitigation approaches like phase-correlated rescanning (Ogata et al 2014), multi-gating (Graeff et al 2014) or tracking (Zhang et al 2014) have been discussed, the vast majority of PBS-PT centers treating moving indications relies on simple motion mitigation approaches. It has been stated that for motion amplitudes < 5mm rescanning might be sufficient to assure robust treatments of moving targets (Jason et al 2018). For larger motion amplitudes techniques are preferred that reduce the motion extent. Respiratory gating and breath-hold techniques are theoretically desirable but logistically challenging, especially in large centers with a single proton source/accelerator and multiple treatment rooms and in patients with poor lung function. While still being investigated, the use of mechanical ventilation, may be a promising way forward for the delivery of proton therapy (Jason et al 2018, Van Ooteghem et al 2019).

4D adaptive therapy: During the course of fractionated radiotherapy, deformational and mass changes associated with regression of the visible tumor occur frequently. These changes often also affect the motion characteristics of the tumor and the surrounding tissue. Prospective pretreatment evaluations only provide multi-scenario predictions without giving a clear patient-specific conclusion for the actual PBS-

PT treatment. To provide robust treatments, especially with highly sensitive proton therapy, adaptive workflows have been suggested (Chang et al 2017).

To facilitate treatment quality evaluation and to support decisions regarding plan adaptation, fraction-wise retrospective four-dimensional (4D) dose reconstruction and accumulation aiming at the evaluation of treatment quality during and after treatment has been implemented (Meijers et al 2019). The described approach considers the influence of changing patient anatomy and variations in the breathing pattern by using treatment delivery log files and breathing pattern records of each fraction as well as most recent available imaging information to reconstruct and accumulate the actual delivered 4D dose. Treatment delivery log are produced by the treatment delivery system and contain, among other data, information about spot position, monitor units (MU) and energy.

Advances to meet the challenges

With the capabilities of new combined imaging and delivery machines (MR-LINAC), the photon therapy world is about to implement daily adaptive treatment regimens (Beaton et al 2019, Corradini et al 2019, Hunt et al 2018) while in PT still rarely more than two or three adaptations are applied throughout the whole treatment course (Mohan and Grosshans 2017, Mohan et al 2017). Time-consuming manual step-wise treatment workflows, the inflexibility of commercial PT equipment (including the treatment planning and oncology information software) and the high diversity in the PT landscape currently prohibits to move towards daily (real-time) or even online (during beam delivery) 4D adaptive treatment approaches. The automation of workflows will play a key element in the further enhancement of 4D planning and delivery of PBS-PT. To make adaptive workflows sustainable, also a broader employment of hypofractionated treatment regimens might be required (see article on "Efficient Treatment Room Utilization").

Imaging capabilities at PT facilities have significantly improved over the last years. CT imaging has been the standard for many years. New PT facilities are often equipped with in-room or near-room CT scanners enabling smooth repeated CT workflows. In the context of daily or online 4D adaptive treatments, daily (or continuous during beam delivery) 4D imaging is required. That cannot be achieved via CT due to the imaging dose. CBCT and MR imaging might be alternatives in this case. While CBCT has been an established technique in photon treatment rooms for almost two decades, the widespread adoption of volumetric image guidance in particle therapy is recent (Landry and Hua 2018). Onboard MR guidance for particle therapy is currently not commercially available but is being actively investigated. A recent review paper (Oborn et al 2015) predicted the accelerated development of hardware and simple prototype systems within a few years and coupled systems integrated with gantries in a decade. To achieve online 4D imaging and subsequently (online) 4D adaptive PBS-PT with either modality, CBCT or MR, further developments are required. (see articles on "Image Guidance" and "Adaptive Therapy")

Automatic synthetic CT generation: Neither CBCT nor MR scans are suitable for proton dose calculations. The clinical implementation of daily or online 4D adaptive PBS-PT will rely on the establishment of automated methods to generate synthetic CTs (sCT) based on CBCT or MR. Especially promising in this context are approaches based on deep learning techniques.

For CBCT deep learning based sCT generation approaches have been investigated (Kida et al 2018). However, for 4D applications, only DIR-based sCT generation methods have been investigated (Veiga et al 2016, Niepel et al 2018) with minor focus on the automation.

Also, sCT generation based on MR images has been investigated for MR-based PBS-PT (Maspero et al 2017, Guerreiro et al 2019). There are no papers yet on 4D MR-based PBS-PT employing deep learning sCT generation approaches with a high level of automation.

Automatic image processing: Automation will also play a major role in contouring for 4D adaptive PBS-PT. Manual delineation on 4DCT is resource intensive due to the high volume of data, which results in longer contouring duration and uncertainties in defining the target. A recent review concluded that auto-contouring for lung tumors is reliable and efficient, producing accurate contours with better consistency compared to manual contours (Wong et al 2019). However, manual inputs were still required both before and after auto-propagation.

Automatic quality assurance (QA): With the employment of 4D adaptive PBS-PT treatment regimens patient specific QA workflows also must become more efficient. The current clinical practice of experimental validation of individual fields will have to be replaced by automated simulations using treatment planning steering files or machine log files and a Monte Carlo (MC) code as independent dose calculation engine (see article on "Treatment Planning"). Concepts towards effective and efficient patient-specific quality assurance for PT have been developed by several groups (Zhu et al 2015, Winterhalter et al 2018, Matter et al 2018).

Concluding remarks

A paradigm shift from manual stepwise to automatic seamless and flexible treatment approaches is required for the clinical implementation of real-time or even online 4D adaptive PBS-PT. 4D imaging (also see section on 'Improving imaging') for treatment planning, 4D treatment planning, 4D QA and 4D treatment verification must be integrated into a real-time 4D adaptive PBS-PT treatment loop to achieve significant improvements in the treatment of mobile cancer indications.

Considering the relative biological effectiveness of protons

Harald Paganetti

Status

Currently tumor prescription doses and organ at risk constraints in proton therapy are based on a generic and constant RBE (relative biological effectiveness) of 1.1 to normalize the physical dose to a photon equivalent. Prescription doses are reported as Gy(RBE). The value of 1.1 was chosen in the early days of proton therapy based on measured RBE values in-vivo relative to Co^{60} in the center of the target volume at ≥2 Gy per fraction for various endpoints such as skin reaction and LD_{50}. It was chosen conservatively to ensure target coverage with prescriptions based on photon experience. Based on an analysis of all published cell survival data in vitro fitted with the linear-quadratic dose response curve (with parameters α and β), the estimated average RBE is about 1.15 in the center of a typical spread-out Bragg peak (SOBP) at 2 Gy(RBE) per fraction (Paganetti, Niemierko et al. 2002, Paganetti 2014). Aiming at a conservative RBE for tumor control, this is in line with the clinical use of 1.1 if an average RBE is to be applied for the target and if clonogenic cell survival in vitro serves as a surrogate for tumor cell kill. For normal tissue the RBE can be substantially higher (Paganetti 2014), which is currently neglected in treatment planning. Elevated RBE values can be expected particularly at the end of range where the linear energy transfer (LET) is increasing when protons decelerate.

Our current knowledge on variations in RBE is largely based on measurements of clonogenic cell survival in vitro. Figure 7 shows a fit through the majority of published experimental data. Various RBE values for endpoints other than cell survival have also been measured in vitro and in vivo but results are inconsistent.

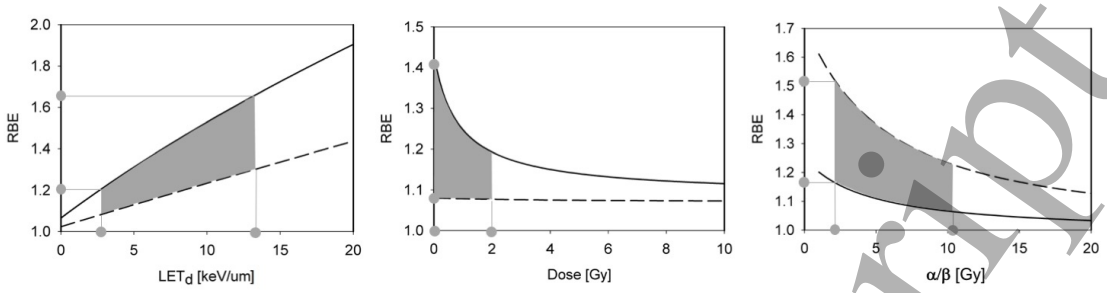

Figure 7: Proton RBE for clonogenic cell survival as predicted by an empirical model (McNamara, Schuemann et al. 2015). Left: RBE as a function of LET_d at 2 Gy for $(\alpha/\beta)_x$ = 2 Gy (solid) and 10 Gy (dashed). Middle: RBE as a function of dose for LET_d=2.5keV/µm for $(\alpha/\beta)_x$ = 2 Gy (solid) and 10 Gy (dashed). Right: RBE as a function of $(\alpha/\beta)_x$ for a photon dose of 2 Gy and LET_d values of 2 keV/µm (solid) and 10 keV/µm (dashed). The grey areas and projection lines highlight the clinically most relevant regions for standard fractionation. $(\alpha/\beta)_x$ refers to the ratio of α and β for the x-ray dose-response curve.

RBE studies based on patient data are inconclusive due to limited data sets and generally low toxicity incidents. There is however increasing concern that proton RBE for normal tissue injuries may be underestimated significantly, leading to unexpected toxicities (Haas-Kogan, Indelicato et al. 2018). There is anecdotal evidence that toxicities seen with protons might be more severe but not more frequent compared to photon therapy. A potential explanation is that patient variability is magnified by RBE effects (Paganetti 2017).

A Task Group report by the AAPM from 2019 concluded (Paganetti, Blakely et al. 2019):

- The current clinical practice of using a constant RBE for protons should generally be maintained but specific clinical scenarios warrant a change in current practice.
- It is important to acquire clinical data to allow the reconstruction of RBE doses and correlate with clinical outcome in both prospective and retrospective studies.
- There are sites and treatment strategies to be identified where variable RBE might be safely utilized for clinical benefit.
- The proton therapy community needs to assess the potential clinical consequences of delivering biologically weighted doses based on LETd and/or RBE and as a function of dose and biological endpoints and assess the potential for harm and benefits associated with the clinical implementation of variable RBE and dose-weighted LETd models into treatment planning systems.
- Experiments are needed to improve our current understanding of the relationships among in vitro, in vivo and clinical RBE and develop recommendations to minimize the effects of uncertainties associated with proton RBE for well-defined tumor types and critical structures. Given the clinical practice of multi-modality treatments, RBE experiments using radiation-drug combinations are needed as well.

A retrospective qualitative and quantitative analyses of late-phase lung-density changes (indicative of asymptomatic fibrosis) for a small cohort of breast cancer patients irradiated to the chest wall showed that late-phase asymptomatic radiographic changes in the lung are associated with a proton RBE potentially even exceeding 3.0 (Underwood, Grassberger et al. 2018) for 2 Gy/fraction. In contrast, for the same endpoint, an RBE on the order of 1.1 was deduced in a cohort of hypofractionated (SBRT) lung cancer patients even though differences in the time course of the inflammatory response after proton compared to photon SBRT were seen (Li, Dykstra et al. 2019). A study on rib fractures in breast cancer patients indicated elevated RBE values at the end of range similar in magnitude compared to clonogenic cell survival data (Wang, McNamara et al. 2020).

Toxicities are a major concern particularly for pediatric patients but it is unclear if RBE variations have a clinical impact (Indelicato, Flampouri et al. 2014, Sethi, Giantsoudi et al. 2014). The potential impact of LET or RBE on brainstem necrosis in patients has been analyzed (Peeler, Mirkovic et al. 2016, Eulitz, Troost et al. 2019). Unfortunately, most studies do not consider the correlation of voxels from the same patient as well as the fact that high LET regions are typically in the periphery of the target where high doses will also increase the likelihood of toxicities. In fact, when patients were analyzed individually, no correlation of elevated RBE in necrotic regions was seen in a cohort of 50 adult patients (Niemierko, Schuemann et al. 2019).

Current and Future Challenges

While of limited value for establishing RBE values in patients, in vitro studies still offer valuable information to our understanding of the basic biological responses to proton and photons radiation. Challenges remain on how to standardize measurements to allow inter-institutional comparison and to limit the large uncertainties in reported data (Durante, Paganetti et al. 2019).

There are currently significant uncertainties in proton RBE values, particularly for in vivo endpoints. Human tumor responses can be measured in vivo using measurements such as the dose for 50% local control of the tumor using human tumor cells implanted in immune-deficient animals but translation into the clinic is questionable. As for patient data, it is unlikely that toxicity data from single institutions will suffice to define RBE for normal tissue endpoints. Due to the uncertainties in RBE, treatment plan optimization based on RBE models is not feasible with clinically acceptable accuracy as patient variability is likely in the same order of magnitude as RBE variations and uncertainties.

Considering typically lower α/β values in healthy tissues, at least for cell survival, as well as lower doses than in the target, one might expect larger RBE values for normal tissue. One reason for our difficulty to assess RBE effects in critical structures from clinical data is the difference in dose distributions after photon and proton irradiations. Most outcome studies are based on normal tissue complication probability (NTCP) models that are mainly based on dosimetric indices extracted from dose-volume histogram (DVH) data (see articles on "Selection of Patients" and "Outcome Modeling"). As proton dose distributions in normal tissue are typically more heterogeneous, estimation of RBE (defined for the same level of effect in a homogeneous area of dose) is challenging.

A value of 1.1 seems appropriate for the tumor if one aims at a conservative value. But RBE depends not only on factors such as fractionation and LET, but also the genomic characteristics of human cells. An important barrier to assessing the biological effects of proton therapy clinically is the paucity of predictive biomarkers (Willers, Allen et al. 2018). Individualized dose prescriptions are desirable, not only in proton but also in photon therapy. (see article on "Biomarkers")

Advances to meet challenges

Even though uncertainties in RBE impacts both, tumor control as well as NTCP, one might expect a bigger clinical impact on NTCP because 1.1 was chosen conservatively. Nevertheless, moving forward, incorporating RBE variations in treatment planning could impact tumor control probability as well. In general, the impact is driven by the steepness of the dose-response curve in the region of interest.

Identifying patients that most benefit from protons (see article on "Selection of patients for proton therapy") should include not only dosimetric but also biological markers identifying individual patients with, for example, high tumor RBE. For instance, a subset of human cancers are expected to show defects in DNA repair pathways that may influence the RBE (Rostek, Turner et al. 2008, Grosse, Fontana et al. 2014, Liu, Ghosh et al. 2015). Additional studies on genomically characterized human cancer cell lines and normal human tissue would be valuable.

One has to keep potential RBE variations amongst patients in mind when comparing doses in clinical trials or when analyzing toxicities and tumor recurrences. With a continued use of a constant RBE the interpretation of outcome data might be misleading when tissue- and spatially variant RBE variations are neglected (Paganetti 2017, Chen, Grassberger et al. 2018).

In order to move towards a true understanding of RBE values in patients, the analysis of outcome data using blood and imaging biomarkers is urgently needed (see article on "Biomarkers"). Particularly for healthy tissue, retrospective investigations on toxicity are currently based on limited number of patients. Furthermore, dose-response relationships should ideally not be solely analyzed based on organ contours but on sub-regions or even voxel-based (Palma, Monti et al. 2019). Moving forward, machine-learning techniques will be a powerful tool particularly when trying to identify radiosensitive sub-regions in organs utilizing the different dose distributions from protons and photons.

Ideally, treatment planning systems would incorporate RBE models and optimize based on RBE-weighted doses. However, as discussed above, our knowledge on mechanisms of normal tissue toxicity prevents this for the foreseeable future. Ongoing efforts on implementing models into treatment planning programs will help estimate potential effects but such models may not be ready for plan optimization.

IMPT allows the delivery of inhomogeneous dose distributions for each field causing plan degeneracy (Lomax 1999). As a consequence, LET distributions can be influenced in IMPT without significantly altering the dose constraints in treatment planning, i.e. dosimetrically equivalent plans can show differences in LET distributions (Grassberger, Trofimov et al. 2011, Fager, Toma-Dasu et al. 2015, Unkelbach and Paganetti 2018). This can be utilized to decrease the efficacy of proton therapy in certain regions of normal tissue, allowing biological dose optimization despite uncertainties in RBE values (Unkelbach, Botas et al. 2016). Translating this method into clinical routine will be beneficial for many patients. The method is largely insensitive to organ and patient specific variations in RBE but, depending on the number of fields, works better for normal tissue than for tumors.

Concluding remarks

A constant RBE of 1.1 is an appropriate average value for ensuring tumor control. However, particularly at the end of range, RBE values are likely higher, potentially affecting normal tissue toxicities. Understanding the difference between photon and proton radiation is now of critical importance because treatment planning vendors may start to prematurely offer RBE based treatment planning using models based clonogenic cell survival data.

Whilst useful in modeling and for understanding biological mechanisms, neither in vitro nor animal experiments will ultimately resolve the issue of how proton RBE should be incorporated clinically for personalized treatment planning. The paucity of clinical evidence indicates that RBE variations maybe on the same order than variability in patient radiosensitivity. Retrospective and prospective outcome studies have to be prioritized. Proton therapy, with its typically more heterogeneous dose distributions compared to photon therapy allows better understanding of volume effects in organs at risk (see article on "Outcome Modeling"). Analyzing proton patients will thus also benefit outcome modeling for conventional treatments.

In the meantime, LET based optimization techniques should be implemented clinically as they allow judging treatment plans based on dosimetric indices while likely reducing the risk for normal tissue toxicities.

Part 3: Improving imaging

Advances in imaging for proton treatment planning

Christian Richter and Patrick Wohlfahrt

Status

X-ray computed tomography (CT) is the undisputed primary imaging modality for proton treatment planning, specifically for dose calculation. The basic methodology, namely the conversion of CT numbers (CTN) derived from a native single-energy CT (SECT) into a quantity relevant for dose calculation (usually the stopping-power ratio, SPR) using a heuristic conversion function (Hounsfield look-up table, HLUT), has kept unchanged since the pioneering years of clinical proton therapy. Nevertheless, in the past decade relevant improvements in CT imaging were introduced (Wohlfahrt and Richter 2020). With iterative reconstruction techniques image noise can be clearly reduced, bearing substantial potential for dose reduction. Still, they have not yet found their way in broad clinical use. In contrast, automated tube current adaptation during acquisition with respect to the patients' anatomy is widely applied, allowing for a constant noise level over different CT slices and effectively reducing imaging dose.

For improved tumor delineation and staging, complementing contrast-enhanced SECT scans and/or positron emission tomography (PET) and magnetic resonance imaging (MRI) are utilized depending on the target. As PET or MRI scans are often performed at different scanners and time points, additional challenges arise from deviations in patient positioning and the required involvement of image registrations.

Notably, CT imaging and CTN-to-SPR conversion protocols vary largely between centers as well as the acquisition and processing of multimodal imaging, introducing severe inter-center variations in dose calculation and delineation (Vinod et al 2016a), potentially interfering with the outcome of multi-centric clinical trials.

Current and future challenges

The reduction of the uncertainty in CT-based SPR and range prediction is a major challenge. The limitations of the HLUT approach are the dominant cause of the nominal range uncertainty in treatment planning which has remained practically unchanged over decades with 3-3.5% of the absolute range (Taasti et al 2018). This is not unfounded, as a recent inter-center comparison, conducted within the European Particle Therapy Network, revealed a 2.6%-2.9% variation in range prediction. For other imaging modalities, like MRI or cone-beam CT, the range prediction accuracy is inferior to CT, currently prohibiting their application for proton treatment planning. Still, with appropriate and required improvements, they could potentially be used in adaptive workflows, as long as the uncertainty in range prediction is smaller than the detected treatment deviation.

An overarching challenge in pre-treatment imaging is an appropriate tissue differentiation, being important not only for accurate SPR assignment, but also for tumor and organ-at-risk segmentation in general.

We define the following long-term goals, which would lead to relevant improvements:

- Range prediction accuracy ≤1% with CT-based imaging
- Automated tissue differentiation for segmentation and appropriate SPR assignment for non-CT imaging

- General improvements in target and organ-at-risk delineation, e.g. using different, purpose-tailored image contrasts and artifact reduction techniques
- Reduction of inter-center variability in SPR prediction and delineation.

Advances in pre-treatment imaging to meet challenges

The clinical availability of dual-energy CT (DECT) scanners in radiology has enabled various applications to improve the diagnostic efficiency and efficacy within the last 15 years and is now often common practice (Agrawal et al 2014). Despite the large research interest in radiation oncology, the first use of DECT for routine proton treatment planning was realized in 2015. Its widespread clinical implementation will become apparent in the near future with increasing evidence for its benefits especially for proton therapy.

Due to a better material differentiation with DECT and thus incorporation of intra- and inter-patient tissue variations, current intrinsic limitations in CT-based stopping-power prediction using an HLUT can be clearly diminished. A relevant reduction of the current range uncertainty of 3-4% to below 2% has already been proven to be clinically feasible with DECT-based direct SPR prediction (Wohlfahrt and Richter 2020) and might be further decreased by improvements in post-processing algorithms (beam hardening and scatter correction, patient size estimation, image smoothing and de-noising). Efforts of CT vendors to provide SPR datasets as input for dose calculation together with dedicated calibration of their CT systems would clearly facilitate the clinical workflow and contribute to a desirable standardization to reduce the current large inter-center variations.

Furthermore, the generation of virtual monoenergetic images after CT acquisition provides different image contrasts - low energy (40-60keV) for increased soft tissue contrast or high energy (120-200keV) to reduce metal artifacts. Separating the distribution of contrast agents in images can further contribute to a better tumor visibility and might even serve as a measure of organ functions or tumor metabolism (functional imaging). The assessment of the optimal application and resulting potential benefit of such additional information for target and organ-at-risk segmentation is currently limited and needs to be comprehensively addressed in future studies.

Nowadays, several DECT acquisition techniques exist (dual-source, dual-layer, fast-voltage switching, dual-spiral). Each of them offers specific benefits and also disadvantages in terms of energy separation, tube current modulation, field of view as well as spatial and temporal differences in projections. Hence, no DECT device for general-purpose application in radiation oncology currently exists and a compromise has to be made based on the respective objective and individual requirements (Wohlfahrt and Richter 2020; van Elmpt et al 2016).

Photon-counting CT systems, the expected next-generation CT technology with energy-resolving detectors, will potentially overcome the mentioned technical limitations of current DECT techniques due to a spectral separation in several energy bins after CT acquisition while maintaining full temporal resolution. Hence, the accurate direct SPR prediction methods developed for DECT will also be unconditionally applicable for body regions with motion-induced anatomical changes. Moreover, projection-based corrections for beam hardening and scattering are thus unconditionally feasible. The availability of multi-dimensional attenuation information (diverse combination of energy bins) seems promising to improve material differentiation, which potentially leads to a higher tissue contrast for tumor and organ segmentation and differentiation of multiple contrast agents. In initial proof-of-concept studies, first prototypes have shown a comparable or slightly better accuracy in SPR prediction and material classification than DECT. Further improvements in spectral de-noising techniques might also reduce the current restrictions in the selection of an appropriate number of energy bins due to unacceptably high image noise. Photon-counting CT can thus become an emerging alternative to DECT

in radiation oncology (Willemink et al 2018).

Range probing, comparing measured and expected depth dose after patient transmission, is a promising tool to verify CT-based range prediction and eventually adapt the CTN-to-SPR conversion (Parodi 2020). Its widespread clinical application would require a smooth integration in proton therapy systems.

The acquisition of three-dimensional stopping-power information using proton CT has been an active focus in research for decades, resulting in first experimental prototypes, which are still in an early stage of development. With the ongoing improvements and clinical implementations of dual-energy CT or photon-counting CT, the potential additional gain in SPR accuracy from proton CT becomes smaller and might be not even clinically relevant at some point. Proton CT would also come with considerable additional costs, would only be applicable for a limited number of body regions due to the current restriction in maximal proton energy (roughly 230 MeV) at most centers, and would reduce the number of patient treatments caused by long acquisition times (several minutes) in the proton treatment room (Johnson 2018). A better scatter prediction already clearly improved the proton CT image quality, but physical constraints limit further improvements in spatial resolution at high-density material gradients and resulting ring and streak artifacts (Parodi 2020). Potential use cases could be patients with metal implants close to the treatment volume (Johnson 2018). However, the continuous improvement of artifact reduction techniques in (multi-energy) x-ray CT could be the clinically sufficient and more cost-effective alternative.

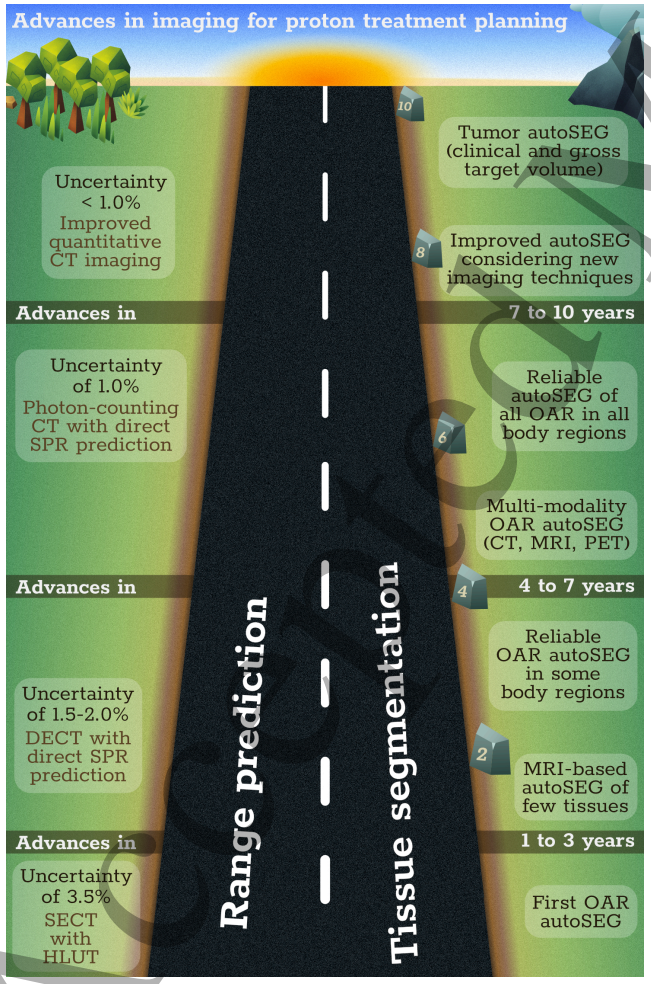

Figure 8: Potential advances in imaging for proton treatment planning, starting from the current situation (bottom). They can be grouped in two tracks – improvements for range prediction accuracy and improvements for tissue segmentation. The proposed periods correspond to the broad clinical application of the respective techniques. (autoSEG= auto segmentation).

MRI offers a broad variety of acquisition modes to differentiate soft tissues and to assess their functional behavior. Combining multi-modality imaging including MRI has proven to reduce intra- and inter-observer variability in delineation (Vinod *et al.* 2016b). The robustness and accuracy of MRI-based material assignment (e.g. synthetic CT generation) for SPR prediction could potentially be improved by using DECT or even proton CT instead of SECT as input. Improvements in geometrical accuracy, motion detection and management as well as accuracy and precision of quantitative MRI are ongoing research challenges (Das *et al.* 2019). Hence, synchronized multi-modality imaging in treatment position is worth aspiring to combine the respective advantages of each technique, decrease registration errors and maximize the patient-specific tissue information available for treatment planning.

Moreover, the technological achievements in imaging enable an accurate and precise experimental determination of the mean excitation energy in

biological tissue samples and patients by combining DECT and range probing or proton CT, respectively. A combination of MRI and DECT or even photon-counting CT can facilitate an even better in-vivo material differentiation and characterization compared to a single-modality approach.

Concluding remarks

The field of pre-treatment imaging has gained substantial translational research interest. DECT, offering substantial reduction of range uncertainty, is currently at the critical cornerstone of broad clinical implementation. In terms of range accuracy, it will set the benchmark for other techniques. Therefore, photon-counting CT will potentially bring benefits for segmentation from tailored image contrasts and enabling direct SPR prediction, as introduced with DECT, for a broader patient population (motion-influenced regions) rather than further decreasing range uncertainties substantially. The investigation and tailoring of photon-counting CT for proton therapy requirements will thus be an exciting field of translational research. For proton therapy applications of all imaging modalities, quantitative imaging in clinical realistic scenarios is key and should be considered in calibration and validation studies, e.g. using phantom setups covering different clinical scenarios.

In summary, we are confident, that not one single imaging modality will fulfill the broad spectrum of radio-oncological needs. Hence, research efforts should focus on finding the best multi-modal synergies. Bringing together imaging and radiation oncology expertise is thus becoming more and more crucial. Figure 8 outlines potential advancements in the next few years.

Conflict of interest statement: The authors received individual funding as lecturer from Siemens Healthineers (2018), which was not related to this study. OncoRay has an institutional research agreement with Siemens Healthineers in the field of dual-energy CT for particle therapy (2016-2020) as well as an institutional agreement as reference center for dual-energy CT in radiotherapy and a software evaluation contract. For the present paper, the authors received no financial support. The other authors report no conflict of interest.

Image guidance

Bas W Raaymakers and Antje C Knopf

Image guided Radiotherapy for improved position verification

In modern radiotherapy, both photon and proton therapy, there is a huge need for imaging; we will argue that the roadmap for image guidance in proton therapy is heavily affected by the experiences in the photon therapy. Image guided radiotherapy (IGRT) is a long standing research and clinical innovation area (Verellen et al., 2007). Imaging in radiotherapy has mainly been developed for improving position verification, that is, to validate the anatomy on the treatment couch relative to the anatomy during treatment planning. The more precise position verification during fractionated radiotherapy treatments, the more conformal dose distributions to the target can be enabled, sparing surrounding healthy tissue from unwanted dose.

A host of imaging modalities is being applied while also surrogates for imaging the target, e.g. using nearby bony anatomy or fiducial markers (Nederveen et al, 2003), are (and can) be used. Most prominent in IGRT is the development and clinical introduction of cone-beam CT (CBCT) acquired from a patient in the actual treatment position (Jaffray et al., 1999). Such volumetric data enables much more precise target identification and with that, patient positioning and is currently in widespread clinical use (Qin et al., 2015).

Recently, in the photon therapy arena, integrated MRI radiotherapy systems were clinically introduced

(Mutic and Dempsey, 2014; Raaymakers et al., 2017). These systems enable MR imaging of patients in the actual treatment position, providing unrivalled, volumetric, soft-tissue contrast data for position verification. If desired, this can be continued during dose delivery for continuous patient monitoring.

Imaging in Radiotherapy for treatment adaptation

The drive for improved imaging during radiotherapy originates from the need for better position verification and has led to daily, volumetric data of the patient from the treatment table. The advent of daily volumetric imaging also led to adaptive radiotherapy (ART; see also article on "Adaptive Therapy"), as by using the daily data the treatment margins can be re-evaluated (Yan et al., 1997). But also, it enables generation of a new treatment plan to account for anatomical changes, e.g. Marchant et al. (2018), instead of trying to re-position the patient according to the pre-treatment planning. Also for such daily treatment adaptation, the hybrid MRI radiotherapy systems will raise the quality of images for clinical decision making on the necessity of adapting. And with their capability to also provide repeated MRI data during dose delivery will drive towards intra-fraction plan adaptation and ultimately real-time adaptive radiotherapy (Kontaxis et al, 2015). Currently, online, or more specifically daily, MRI based adaptation is an accepted clinical reality (Henke et al., 2018).

Also, recently a new artificial intelligence driven eco-system for adaptive photon beam therapy is commercially launched for clinical introduction (www.varian.com/ethos). This workflow uses CBCT as an input, so it lacks the soft-tissue contrast of MRI, but it provides an integrated, fast, adaptive workflow, which enables 15 minutes full adaptive radiotherapy treatment fractions for certain tumor sites.

Which imaging modality will be most suitable for which tumor site, the frequency of adaptation and the delivery on the promise that this will lead to more hypo-fractionation needs to be established from clinical experience. The desire for improved position verification and more frequent treatment adaptation will jointly require better, and more frequent, imaging.

Roadmap for image guidance in Proton therapy

The introduction of the imaging and adaptive innovations has mainly taken place in the photon therapy clinic, widespread adoption in proton therapy is lagging for these developments (Lomax, 2018). For proton therapy both position verification and treatment adaptation are very relevant for improving treatment accuracy. IGRT developments from photon beam therapy are being translated to proton therapy, e.g. CBCT guidance is being used more and more frequently in proton therapy (Landry and Hua, 2018). In essence the roadmap for imaging in proton therapy, where it concerns anatomical imaging for position verification and for adaptation, is similar to that of photon therapy. A nuance is that proton therapy is considered high-end radiotherapy, both due to its ability to stop the treatment beam posteriorly of the tumor to spare the surrounding tissues and due to its costs. To live up to this expectation, imaging in proton therapy should be at least of similar quality as the state-of-the-art imaging used in photon beam therapy. This implies that the roadmap should aim to obtain real-time, volumetric, high soft-tissue contrast imaging to enable position verification, dose reconstruction and treatment adaptation as MRI provides for photon beam therapy.

An additional requirement for imaging in proton therapy is to verify not only the geometrical location of the target, but also the proton beam range in the patient (Knopf and Lomax, 2013). Proton radiography (Hammi et al., 2018), PET imaging (Parodi et al., 2007) and prompt gamma imaging (Hueso-González et al., 2016) are being explored for treatment verification (see also article on "In vivo range verification").

Thus, patient imaging during treatment initialization, when the patient is on the treatment table, should yield both the anatomical and stopping power data (see also article on "Advances in imaging"). For proton therapy both topics are active fields of research (Mackay et al., 2018; Poludniowski et al., 2015).

Alternatively, these imaging data can be used for plan adaptation (see also articles on "Adaptive Therapy" and "Treatment planning"). By combining the data, the stopping powers of the various tissues in the anatomy can be determined, while all relevant structures for (re-)planning can be identified on the anatomical data. Once this is done, the challenge of re-planning is very similar as for photon beam therapy, of course with the difference being a proton therapy treatment planning system, for instance by daily CBCT based re-planning. For proton therapy, daily CBCT has recently become a clinical reality while in-vivo range determination by prompt gamma imaging is awaiting wider clinical employment and investigations. So daily CBCT based plan adaptation is something that can be explored currently. However, to match the state-of-the-art image quality in photon beam radiotherapy, MRI for anatomical imaging should be on the roadmap.

MRI guided proton radiotherapy

In MRI guided proton therapy, the need for stopping power data is still equally much needed as with any other anatomical image guided modality. If the stopping power data is coupled to the MRI, the repeated, ultimately real-time, anatomical data can be used to track the entire anatomy during beam delivery. Actually, for proton therapy, with its sharp dose fall off around the Bragg peak, this might be even more relevant than for photon beam therapy. MRI guidance in the context of proton therapy has been proposed (Raaymakers et al., 2008) and is being explored experimentally (Schellhammer et al., 2018) and *in silico* (Oborn et al., 2017). This is not near clinical reality, still, as these developments to realize real-time adaptive MRI guided dose delivery in photon beam therapy are advancing, this should be on the roadmap for proton therapy too.

Concluding remarks

On-line adaptive radiotherapy is a new clinical reality in the photon radiotherapy world. Volumetric anatomical imaging in treatment position as well as a transition to more seamless, automatic workflows enables the clinical deployment of online adaptation. For proton therapy to keep up with this reality, the road map should include in-vivo range determination by prompt gamma imaging and volumetric anatomical imaging of the patient in treatment position on the treatment table. CBCT is a good starting point for improving position verification and daily plan adaptation.

MRI should be on the roadmap as it provides unequalled anatomical imaging for position verification but also anatomical tracking of both target and all surrounding structures. These features will drive a paradigm shift in photon beam radiotherapy towards online, and ultimately real-time, adaptive radiotherapy, something that will also affect the expectation of proton therapy. A starting point for using MRI in proton therapy is to include more MRI in the preparatory phase of treatment planning to investigate the coupling of range imaging and MRI.

Conflict of interest

Bas Raaymakers received financial research support from Elekta AB, Sweden for work on developing MRI guided photon therapy.

Part 4: Improving patient selection

Model-based selection of patients for proton therapy

Johannes A. Langendijk and Stefan Both

Status

Beginning 2018, proton therapy (PT) has been clinically introduced in the Netherlands. In 2015, the Royal Netherlands Academy of Arts and Sciences (KNAW) concluded that an RCT (randomized controlled trial) is not always the most optimal study design for evaluating the benefit of technology and that for different types of new applications, different research approaches are required (Langendijk et al 2018). Alternatively, for the selection of patients for PT, the so-called model-based approach was introduced, which has been accepted by the National Health Care Institute (ZiN) (Langendijk et al 2013; Widder et al 2016). Consequently, when adult patients are selected according to a model-based selection procedure, PT is insured care and will be fully reimbursed.

Model-based selection is developed to identify patients that may benefit from PT in terms of reducing radiation-induced side effects. It relies on three basic principles: 1) the definition of the target volumes and fractionation schedules is similar to what would be used when patients are with photons, assuming equivalent tumor control; 2) the dose to the most relevant organs-at-risk (OAR) in the proton treatment plan should be lower than that obtained with photons (i.e. ΔDose), and: 3) this ΔDose should translate into an expected decrease in normal tissue complication probabilities (i.e. ΔNTCP). To translate ΔDose into ΔNTCP, NTCP-models are used, i.e. prediction models that describe the relationship between the dose distribution in OAR and ` risk on radiation-induced toxicity.

For each tumor site, the criteria for model-based selection are described in detail in National Indication Protocols for PT (NIPP), which contain general eligibility criteria (e.g. curative treatment), a detailed description of the NTCP-models that can be used for model-based selection as well as the ΔNTCP-thresholds to determine if patients qualify for PT. To assess ΔNTCP, an in-silico plan comparison is performed comparing the best dose distribution with photons with the best dose distribution with protons. Based on these dose distributions, NTCP-profiles for photons and protons and subsequent ΔNTCP are produced to assess if the criteria are met (Figure 9).

For selection of head and neck cancer, three NTCP-models are used (moderate-to-severe patient-rated xerostomia, physician-rated dysphagia grade ≥ 2 and tube feeding dependence). For breast cancer patients, an NTCP-model for acute coronary events derived from the Darby model is used (Darby et al 2013).

Current and future challenges

Model-based selection requires high quality NTCP-models, preferably validated in independent datasets to test their generalizability of these NTCP-models (Langendijk et al 2018).

However, for many tumor sites, the numbers of NTCP-models that meet these criteria is limited or are currently not available. E.g., the literature review on NTCP-models in low grade glioma patients did not reveal any NTCP-model that could be used for model-based selection. So far, these tumors, selection strategies should be applied. In the case of low grade glioma, selection is currently based on identifying patients with the most favorable prognosis (i.e., 5-years overall survival > 50%) who are at risk for long-term neurocognitive decline. Second, virtually all NTCP-models published so far are based on photon-based radiation techniques. However, NTCP-models can be affected by changes in the irradiation technique. Therefore, it is paramount to continuously update and validate these NTCP-models in subsequent patient cohorts treated with new techniques. The challenge here is to create an infrastructure support for prospective collection of high quality data, allowing for development and validation of multivariable NTCP-models for comprehensive sets of radiation-induced toxicities.

Another important challenge is related to the clinical implementation. Model-based selection as part of routine clinical practice is completely new, relatively complex and resource intensive, especially if patients are referred from other centers. In head and neck cancer, approximately 30-40% qualifies for PT based on the plan comparison, while in breast cancer this is only 5-10%. Performing plan

comparisons in all these patients is logistically not feasible. Therefore, tools to select patients in which a plan comparison is indicated are desperately needed.

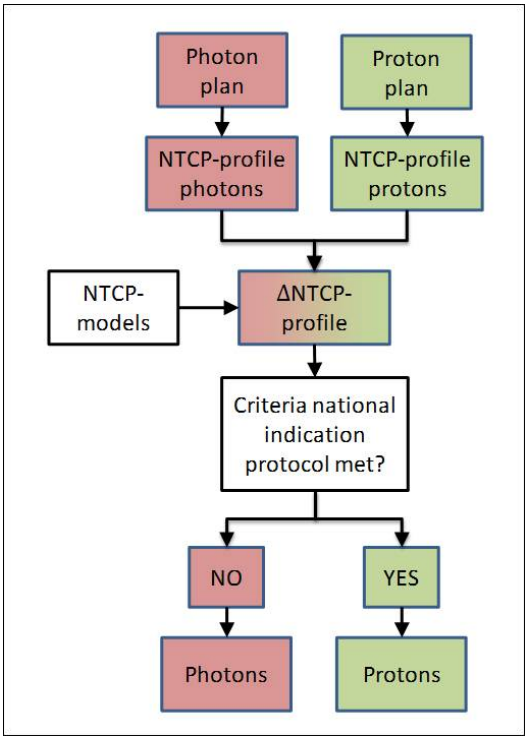

Figure 9: Schematic overview of model-based selection procedure

Advances in Science and Technology to Meet Challenges

Along with the introduction of PT in the Netherlands, a nationwide PT research infrastructure (ProTRAIT) is currently under construction to support prospective data collection of all patients treated with PT. ProTRAIT aims to setup PT registries developing tools for radiotherapy that will enable an unprecedented combination of both DICOM-RT and clinical/follow up data for integrated analysis. More specifically, ProTRAIT: 1) defined tumor-specific registries for patient groups that are with PT; 2) setup an IT infrastructure supporting the model-based approach on a national scale by harmonizing data acquisition (clinical, DICOM RT); 3) makes data FAIR (Findable, Accessible, Interoperable and Reusable) and links data from different sources and centers; 4) develops an IT infrastructure that supports fast development, update and external validation of NTCP models, and: 5) deploys an IT infrastructure to support quality assurance in radiotherapy for clinical trials. This infrastructure will also be used for collecting data from photon-treated patients for the development and validation of NTCP-models. The ProTRAIT-project will be completed in 2021. This approach will be further extended on a European scale by the European Proton Therapy Network (EPTN).

To enhance further adoption of the model-based approach, clinical workflows need to be simplified and automated whenever possible. First, heterogeneity across centers in contouring OAR may jeopardize fair plan comparisons between photon and proton plans even when international guidelines are available (Brouwer et al 2015). Automated contouring using deep learning techniques derived from artificial intelligence (AI) has emerged useful to improve performance resulting in smaller dose differences compared to manual contouring and marked reductions of delineation times (van Dijk et al 2019). AI solutions for automated photon-based treatment planning are currently developed and clinically deployed, holding the promise to significantly reduce treatment planning time while eliminating large variations in treatment planning performance across centers, as was recently shown in a Dutch benchmark study using predefined regions of interest in one patient (Verbakel et al 2019). Similar automated planning tools are under development for PT, however this is a more challenging task especially when combined with robust optimization (Kierkels et al. 2019).

To reduce the number of unnecessary plan comparisons, attempts are made to use knowledge-based planning solutions (see article on “Treatment Planning”), treatment planning based on prioritizing prescription goals or AI, to improve the accuracy of identifying patients who will qualify or not for PT prior to a plan comparison in different phases of the preparation workflow (Delaney et al 2017; Wilkens et al 2007). As validated NTCP models become available for various treatment sites and combined NTCP profiles start to be used, a transition from NTCP evaluation to NTCP evaluation and optimization becomes more feasible. This may further improve efficiency of clinical workflows.

Concluding Remarks

In the Netherlands, patients are selected for PT using a model-based approach provided that PT is intended to reduce radiation-induced side effects with similar loco-regional control. The main challenge is to develop and validate multivariable NTCP-models to enrich ΔNTCP-profiles that can be used for patient selection for both photons and protons. To this purpose, a nationwide IT research infrastructure is created (ProTRAIT). In addition, clinical workflows should be optimized and automated to facilitate logistic hurdles in patient selection and referral.

Outcome Modeling for Proton Therapy

Harald Paganetti

Status

Both tumor control probability (TCP) as well as normal tissue complication probability (NTCP) models are constantly being refined. As normal tissue sparing is one of the main dosimetric advantages of proton therapy, it will likely not be tumor control but rather normal tissue complication differences compared to photon therapy that will determine its benefits. Several retrospective and prospective studies have identified areas where proton therapy does indeed make a significant clinical impact and reduces toxicities but there are also studies where an advantage was not seen. Independent of the delivery method, proton therapy reduces the integral dose (total energy deposited in the patient) by a factor of 2-3 compared to photon techniques (Lomax, Bortfeld et al. 1999). While this reduces the overall dose to healthy tissue, it may not translate into a toxicity advantage depending on the dose-limiting endpoints and how the dose is distributed.

Models based on parameters deduced from clinical studies are often used to predict clinical outcome (Semenenko and Li 2008). For instance in lung, single parameters are extracted from DVHs such as V20 and mean lung dose to predict radiation pneumonitis in photon therapy (Fay, Tan et al. 2005, Marks, Bentzen et al. 2010). However, dose volume parameters deduced from photon treatments might not apply to proton treatments with more inhomogeneous dose distributions (Tucker, Xu et al. 2019). For instance, dose to the lower parts of the lung is more predictive of radiation pneumonitis than dose to the upper lobes (Seppenwoolde, De Jaeger et al. 2004, Hope, Lindsay et al. 2006).

Proton therapy outcome relative to photon therapy is also affected by RBE considerations (see article on "Relative biological effectiveness"). The current RBE formalism assumes that normal tissue complication probability estimates for proton therapy can be based on scaled photon doses in each CT voxel. There is increasing concern that the RBE for normal tissue injuries may be underestimated, leading not only to more but to more severe toxicities than expected from analyzing dosimetric indices (Haas-Kogan, Indelicato et al. 2018). Toxicities in proton therapy could be more affected by inter-patient variations leading to a wider distribution of the severity compared to photon radiation (Paganetti 2017), which would also impede comparisons between cohorts. Predicting in vivo normal tissue responses after radiotherapy using in vitro cellular biomarkers and radiosensitivities assumes a direct correlation of toxicity with radiation induced DNA damage, neglecting, for instance, the involvement of cytokine-mediated multicellular interactions in radiation response (Stone, Coleman et al. 2003). As discussed in the roadmap article on Systemic effects in Proton Therapy, the integral dose may even influence toxicities via impacting immune response.

Current and Future Challenges

Most outcome studies apply NTCP models that are based on dosimetric indices extracted from DVH data. Even more simplistic and thus complicating IMRT/IMPT comparison, the majority of current approaches for modeling of radiation dose-response rely on single parameters such as mean dose or

generalized effective uniform dose to an organ-at-risk represented by a single segmented (contoured) region-of-interest (Yorke 2001, Troeller, Yan et al. 2015). Data suggest that such NTCP models might fail to discriminate even at the level of physical dose whether an individual proton plan is effectively ranked superior to a comparison photon plan (Chaikh, Calugaru et al. 2018, Kobashi, Prayongrat et al. 2018).

In addition, non-local effects are complicating comparisons: for instance parotid tissue is treated for dose-constraint purposes as having uniform RBE, and thus even tissue radiosensitivity across the organ. Irradiation of the rat parotids with a proton beam showed that tolerance of the parotids to irradiation of a focal subvolume "shower" (van Luijk, Pringle et al. 2015) is reduced by a sub-tolerance dose administered to a larger, surrounding volume "bath" (van Luijk, Faber et al. 2009). There might even be fundamental differences in normal tissue toxicities between proton and photon radiation due to not only the differences in the distribution of dose, which could interact with varying sub-region sensitivity across a larger organ, but also due to not well understood variations in RBE for normal tissue toxicities.

The questions of photon-based outcome modeling and RBE need to be considered also for model-based trial concepts, where a threshold restricts the cohort to theoretically favorable subpopulations (see article on "Model based selection"). Toxicities in head and neck cancer have been used as examples for model-based trial approaches in proton therapy (Langendijk, Lambin et al. 2013) but photon-based NTCP models can be insufficient for individual patient plan selection (Blanchard, Wong et al. 2016).

Advances to meet challenges

Research is ongoing into defining more relevant dosimetric parameters that go beyond mean doses or even DVHs. Voxel-based approaches aim at exploring local dose differences associated with radiation toxicities. A voxel-based analysis of dose distributions can thus identify sensitive areas in organs independent from drawn contours (Han, Lakshminarayanan et al. 2019, Palma, Monti et al. 2019, Monti, Paganelli et al. 2020, Palma, Monti et al. 2020). Figure 10 shows an example illustrating where patients with radiation-induced lung damage received a significantly greater dose in parenchymal regions although overall low doses were delivered.

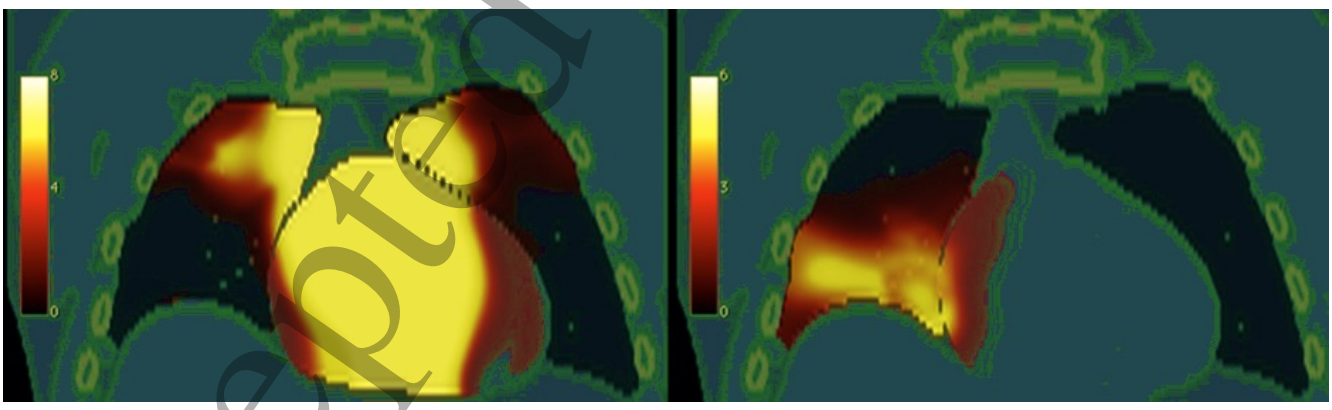

Fig. 10: Left: Significance map (–log p) of BED differences between IMRT and PSPT patients (spared regions), Right: significance map (–log p) of BED differences between patients who developed radiation pneumonitis and who did not (sensitive regions) (adapted from (Palma, Monti et al. 2019)).

Refinements of outcome models based on these concepts benefit from data deduced from inhomogeneous dose distributions such as delivered in proton therapy. This will lead to a better understanding of the mechanisms of normal tissue toxicities which will also improve conventional photon therapy. Furthermore, this will increase our understanding for which patient cohorts and treatment sites the advanced dose shaping capabilities of protons can be utilized towards a true outcome

benefit.

While these approaches will improve our understanding of toxicities, outcome models relying on dose alone are unlikely to effectively predict toxicities (Rancati, Fiorino et al. 2011). In addition to dose distributions, the use of blood and imaging biomarkers to quantify radiation injuries can be incorporated to inform predictive models, e.g. by leveraging deep learning methods to incorporate biomarkers and other confounding factors into a voxel-based dosimetric analysis. To consider the multidimensional nature of NTCP predictions, multivariable logistic regression modeling frameworks have combined dose-volume metrices with other patient- or disease-based prognostic factors using data-driven modeling to improve outcome prediction (El Naqa, Bradley et al. 2006, Lee, Chao et al. 2014, El Naqa, Kerns et al. 2017). Risk factors can be included directly as features in data-driven approaches (Ibragimov, Toesca et al. 2019, Ibragimov, Toesca et al. 2020). Such approaches are likely more promising than efforts to base outcome modeling on mechanistic input parameters (Rutkowska, Baker et al. 2010).

Concluding remarks

This article did focus on NTCP because this might be more relevant and specific to proton therapy as long as prescription doses in proton therapy are identical to those in photon therapy (except for RBE correction). However, moving forward, both hypofractionation and re-irradiation will increasingly being used in proton therapy. This will cause proton specific aspects of TCP modeling to become more important. Note also that with re-irradiation becoming more common (a treatment where lower integral dose is particularly important), NTCP models need to be extended to scenarios in which multiple targets receive dose, or normal tissues are re-irradiated due to new lesions in the same organ.

Outcome modeling approaches for normal tissue toxicities can be divided into three classes (and combinations of them). One is mechanistic effect modeling, which is currently not feasible with clinically relevant accuracy. The second type are phenomenological analytical models based on clinical data, which are currently standard for most studies. These have now evolved by incorporating confounding factors and imaging biomarkers. The third approach are machine learning concepts which will play a bigger role to either complement our current outcome formalisms or even replace them altogether. Voxel-based dosimetric analysis as well as the incorporation of biomarkers will make this transition likely. These efforts will of course impact both photon and proton outcome modeling. However, proton therapy will play a large role in research towards novel modeling approaches as the more inhomogeneous dose distributions and their variety will be advantageous for refining outcome models based on a better understanding of intra-organ sensitivity.

The aim will not be to develop proton-specific NTCP models but to challenge the current NTCP modeling concepts that are mainly based on two-dimensional dosimetric parameters and pre-defined structures and volumes of interest.

Biomarkers in Proton Therapy

David R. Grosshans, Simona F. Shaitelman and Gabriel O. Sawakuchi

Status

Technological advancements in radiation therapy have improved our ability to target and eradicate gross disease. We have also gained an increased appreciation for the potential side effects of radiation therapy, quantified the magnitude of such effects, and documented their negative influence on quality of life for cancer survivors. However, our ability to predict whether tumors will respond to treatment or patients will suffer from treatment-induced toxic effects is limited largely to classical dose–response

relationships, and little is known about the susceptibility of individual patients and their tumors.

Efforts to improve tumor control have included various dose escalation or fractionation strategies, as well as sequential or concurrent treatment with chemotherapies or other antineoplastic agents. Such strategies have been successful in increasing tumor control rates, albeit at the cost of additional toxicity; however, we remain unable to predict either tumor response or radiation-induced toxic effects for individual patients. In part, this is because technological advances in radiation delivery have been driven by anatomic targeting based solely on physical factors. However, the intrinsic physical properties of how radiation interacts with cells and tumor tissue set a theoretical limit on the anatomic targeting of radiation. Currently, we know that radiation response is affected by various biological factors including genomics (Scott et al., 2017), the microbiome (Reis Ferreira et al., 2019) of tumor and normal tissues, the immune system (Twyman-Saint Victor et al., 2015), and the tumor microenvironment (Vaupel, 2004). Finding predictive features within these biological factors will add another dimension for predicting response or toxicity.

The term "biomarker" refers to a measurable and quantifiable indicator of response. It stands to reason that maximizing cure rates and reducing toxicity will require biomarkers based on unique biological factors to predict tumor response or treatment-induced toxicity for individual patients, whether treatment is with radiation alone or in combination with molecularly targeted therapies.

An example of the need for biomarkers is highlighted by proton therapy, a prime example of physics-driven technological advancement in radiation oncology for which biomarkers have not been explored. Proton therapy is expensive, and clinical evidence indicating its superiority to modern photon therapy is lacking. Therefore, biomarker development is crucial to facilitate the selection of appropriate patients for proton therapy and thereby provide high-level clinical evidence supporting its use.

Current and Future Challenges

Most biomarker studies related to radiation therapy have focused on identifying predictors of tumor response to photon-based therapies (Scott et al., 2017; Yard et al., 2016; Manem et al., 2019). Such predictive knowledge would allow stratification of patients into discrete groups based on likely response, and would allow treatment intensification or de-intensification or even prospective customization of dose and fractionation for individual patients. Although the potential for biomarkers is great, our understanding of factors associated with radiation response, even for photons, is limited. However, examples are emerging. A prime example of a potentially clinically useful predictive biomarker includes the human papillomavirus (HPV) status for patients with head and neck cancers. HPV-associated tumors have relatively high cure rates (Ang et al., 2010), and dose de-escalation strategies that lead to less radiation-induced toxicity are now being assessed. Other attempts made to predict radiation sensitivity include assessing the clonogenic survival or DNA damage response of tumor cells cultured from individual patients. However, these approaches are labor-intensive and time-prohibitive for enabling rapid changes to clinical care plans.

Genomic techniques may hold more promise for this purpose (Scott et al., 2017; Yard et al., 2016; Manem et al., 2019). Genomic biomarkers use genomic features of tumor or normal tissue samples in an attempt to identify patterns indicative of tumor response to radiation or radiation-induced toxicity. Tools to identify signatures of response are evolving rapidly and include newer bioinformatics techniques as well as the analysis of new publicly available datasets (Scott et al., 2017; Yard et al., 2016; Manem et al., 2019).

In addition to blood or genomic biomarkers, imaging biomarkers may also be of great utility (Elhalawani et al., 2018). Imaging in radiation oncology has historically been used for target delineation, verification of positioning, and response assessment. However, functional imaging modalities such as magnetic

resonance imaging may also provide insight into the biology of how tumors (or subsections of tumors) and normal tissues of individual patients respond to radiation, which may relate to intrinsic radiation sensitivity. Like genomic biomarkers, imaging biomarkers may allow identification of patients who might benefit from dose escalation, thereby improving local control.

With respect to proton therapy, for practical purposes the biological effects of protons and photons have been assumed to be relatively similar, with protons on average being 10% more biologically effective than photons; thus, a relative biological effect (RBE) value of 1.1 is used to normalize physical dose for treatments (see article on "Relative biological effectiveness"). However, at the cellular level, the patterns of proton-induced DNA damage differ from those of photons, particularly in areas of high linear energy transfer (LET). In studies of cell lines, these differences correlate with decreased clonogenic survival, resulting in RBE values approaching 1.8, even in areas proximal to the Bragg peak. More importantly, different cancer cell lines of the same histologic type have a large range of RBE values (Liu et al., 2015). These differences in response likely arise from intrinsic genomic differences, such as capacity to repair clustered DNA damage, that are more likely to be affected by protons (Bright et al., 2019). While in most cases such alterations are likely limited to the tumor itself, individual patients with particular germline mutations, which also affect normal tissues, must be carefully identified to avoid adverse radiation-induced toxic effects that could be induced by protons because of their higher RBE. The identification and quantification of predictive biomarkers of tumor and normal tissue response to protons would allow practitioners to identify patients whose cancer would be best treated with protons (aside from favorable dose distributions alone) while reducing toxic effects (Figure 11). Other tumors with certain forms of DNA repair defects may be equally sensitive to photons and protons, and therefore use of protons for such tumors would be based on protons' superior dose distribution. On the other hand, tumors that are radiation-resistant to photons might be better suited for treatment with heavier ions, in which the still-higher LET may overcome resistance. Genomic approaches seem the most plausible to achieve this goal.

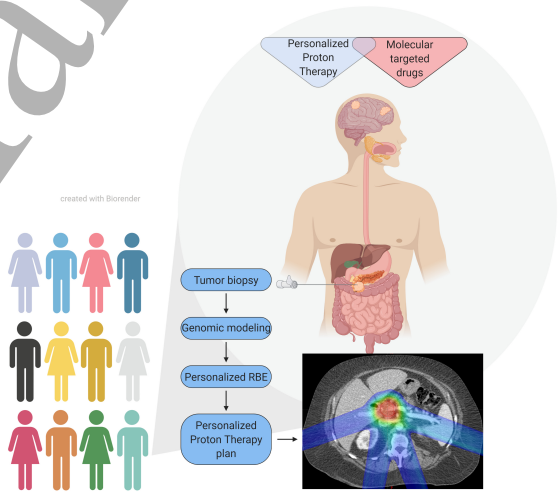

Figure 11: Illustration of a genomic biomarker framework to predict tumor response to proton therapy.

Advances Needed to Meet Challenges

The primary challenge for all biomarker development is the need for large patient or preclinical datasets, with accurate response data coupled with genomic or other relevant information (see article on "Outcome Modeling"). Although some datasets are being developed for photon radiation (Scott et al., 2017; Yard et al., 2016; Manem et al., 2019), very few are available for proton therapy. Hence, a necessary step will be the development of preclinical and clinical datasets of patients treated with proton therapy. From a preclinical perspective, cellular response data can be obtained, albeit at high cost. Clinical datasets will be even more challenging, given the limited number of clinical proton centers and the general lack of banked tumor samples for future study. Successful advancement of proton (or particle) therapy will require significant funding and collaboration between numerous investigators. As sample acquisition and annotation improve, so will data analysis techniques such as machine learning and artificial intelligence, which may even reduce the number of data points required. Another urgent need is information for predicting normal tissue toxicity, even for photons. However, investigations of normal

tissue toxicity face greater obstacles, as severe radiation toxicity events are thankfully relatively rare.

Concluding Remarks

A perceived challenge for biomarker studies is the prospective analysis of candidate biomarkers. However, the advent of proton and particle therapy may eventually necessitate the use of predictive biomarkers for selecting patients who will derive meaningful benefit from these modalities. Predictive biomarkers are now being used in trials of new anticancer pharmaceutical agents to select patients who will respond to those agents, which essentially biases such studies in favor of a successful trial. Future biomarkers may allow us to predict tumor and normal tissue responses that in turn may indicate an increased biological response to particle therapy, including protons. This, along with refinement of delivery technologies, would allow proton therapy to reach its full potential in smaller, more efficient trials.

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Systemic effects of proton therapy

Harald Paganetti and Clemens Grassberger

Status

The lower integral dose and reduced toxicity of proton therapy offers an opportunity to explore clinical trials combining proton therapy with intensified systemic therapy and/or dose-escalated radiotherapy. Proton chemo-radiotherapy administered concurrently has been shown to be associated with significantly reduced acute adverse events that caused unplanned hospitalizations, with similar disease-free and overall survival (Bauman et al. 2019). While radiation therapy has mostly been combined with surgery and/or chemotherapy up to now, the cancer treatment landscape has changed significantly with the addition of targeted agents as well as immune-modulating therapies in recent years. Thus, even though combinations of radiation and drugs are the standard of care, the field is advancing quickly as new drugs and trial results become available. The combination of radiation with biological agents can have tumor-directed as well as toxicity-related effects, and interactions can be additive, supra-additive, or infra-additive. There is a paucity of clinical data regarding differences in proton vs. photon outcomes in the setting of targeted therapy. However, there is emerging data that differences in signaling pathways with proton therapy may help to overcome radioresistance (Konings *et al.* 2020).

For instance, radiation therapy has both immune-stimulatory and immune-suppressive effects. The interaction of radiation with the immune system is complex and often difficult to interpret as radiation has detrimental effects not only on tumor infiltrating lymphocytes, lymphatic vessels and nodes, but also on circulating lymphocytes in the blood (Kaur and Asea, 2012). In addition to baseline lymphopenia and other markers of inflammatory status in solid tumor patients, radiation-induced lymphopenia (RIL) develops in up to ~70% of radiation therapy patients (Ellsworth, 2018; Yovino et al., 2013; Wild et al., 2016). In some photon radiation techniques (such as volumetric modulated arc therapy (VMAT)), large

volumes of tissue receive low and intermediate radiation doses, which have shown to impact the circulating lymphocyte population (Tang et al., 2014). High-grade RIL has been widely associated with poor overall survival, disease recurrence, occurrence of distant metastases, and reduced pathologic complete response rates in a variety of tumors (Grassberger et al., 2019).

Proton therapy differs from photon therapies in the distribution of the low dose bath to the body outside of the planned treatment volume and also in the treatment delivery time within a fraction. Figure 12a highlights the dosimetric differences for an intracranial tumor treated with either photon and proton therapy, which causes differences in dose to circulating lymphocytes (Fang et al., 2018; Ko et al., 2018). In studies on esophageal cancer it has been shown that patients treated with proton therapy have a >50% lower probability of developing grade 4 RIL compared to patients treated with IMRT (Routman et al., 2019), an endpoint correlated to overall survival (Davuluri et al., 2017). Due to the lower integral dose, patients treated with protons had ~70% less grade 4 RIL compared to IMRT. However, this does depend both on target location relative to major vessels as well as differences in integral dose, and was not observed in a study of 150 patients with oropharyngeal cancer (Jensen et al., 2017).

In addition to the radiation therapy modality, fractionation also affects the dose to the blood and the lymphocytes, thus possibly impacting outcome (Plowman, 1983; Crocenzi et al., 2016; Ko et al., 2018). Lymphocyte sparing radiation therapy was suggested because stereotactic body radiation therapy resulted in significantly less RIL in pancreatic cancer (Wild et al., 2016) and liver cancer (Gustafson et al., 2017). Smaller target volumes and hypofractionated regimens may be associated with higher post-treatment lymphocyte counts. It has been estimated that during a conventional 30-fraction treatment with 2 Gy/fraction to an 8-cm diameter planning target volume, 95% of circulating blood receives >0.5 Gy with a mean dose to circulating blood of >2 Gy (Wild et al., 2016) (Figure 13). Field size and dose rate effects on lymphopenia for solid tumors have been explicitly studied (Ellsworth, 2018). Not only dose to circulating lymphocytes but also dose received by tumor infiltrating lymphocytes, bone marrow, the lymphatic system and other lymphocyte reservoirs need to be considered.

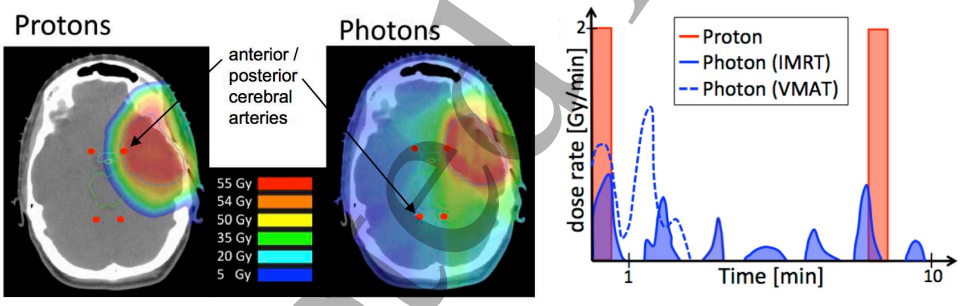

Figure 12: a, left: Treatment plans for an intracranial tumor (left: IMRT; right: proton therapy). b, right: Schematic illustration of the dose rate during a typical treatment for passively scattered proton therapy (red) and photon therapy (blue).

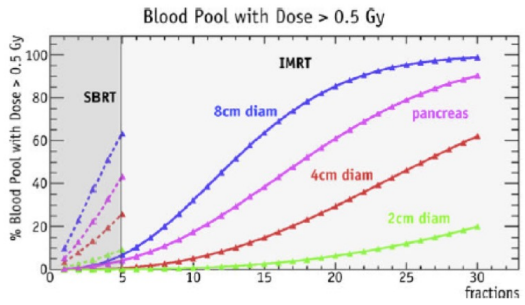

Figure 13: Lymphocyte sparing in pancreatic cancer using conformal treatments (Wild et al., 2016) (with permission).

In addition to radiation therapy impacting immune response, it also interacts with immune therapies. As radiation therapy has both local and systemic effects on the immune system, the combination of radiation therapy with immunotherapy represents a potential tool to maximize immune response and thus the efficacy of immune therapies (Kalbasi et al., 2013; Salama et al., 2016; Seyedin et al., 2015; Wang et al., 2018; Vatner et al., 2014).

Current and Future Challenges

Particularly in terms of tumor response, it is important to understand the interaction of protons with those drugs that target specific DNA damage or repair pathways. For instance, drugs can provide tumor cell selective radiosensitization to be combined with radiation therapy (Morgan and Lawrence 2015). As discussed in the section on "Relative Biological Effectiveness" the proton RBE depends on DNA repair pathways and as such also the interaction of protons with drugs targeting DNA damage or repair can influence the RBE. Similarly, new agents that have overlapping toxicities with radiation have to be studied carefully to confirm the validity of toxicity response models, for example pneumonitis in the case of immune checkpoint inhibitors with thoracic radiation therapy (Hwang et al. 2018).

In addition to standard cytotoxic agents, the efficacy of proton therapy has to be analyzed in the context of immune therapies. Clinical data indicate that the low dose bath does affect the degree of RIL (Rudra et al., 2018). On the other hand, it has been suggested that low dose whole-body irradiation might improve outcome after subsequent treatment regimens due to radiation induced antigen release (Liu et al., 2010). In addition to dose-volume considerations, a faster rate of irradiation enables a larger fraction of circulating lymphocytes to be spared. The proportion of lymphocytes in circulation, and consequently at risk of being irradiated, might dictate the degree of systemic immune exposure. This is especially important for tumors that are close to major vessels, such as esophageal or centrally located lung cancers. Figure 12b illustrates dose rates to a voxel close to the target for a 7-field IMRT, a VMAT, and a passively scattered proton therapy plan. Intensity modulated proton therapy with its high degrees of freedom might offer new approaches to treatment optimization in the context of immune response or immunotherapies.

To better understand the effect of the radiation dose bath on the immune system, we need more data on the presumably high relative radiosensitivity of lymphocytes in terms of cell kill and functional inactivation (Vandevoorde et al., 2016; Radojcic and Crompton, 2001). The impact of radiation not only on circulating lymphocytes but also on lymphatic vessels, tumor infiltrating lymphocytes and immune-related signaling by normal tissues around the tumor needs to be better understood. Furthermore, predictive models of lymphocyte depletion rates and lymphocyte nadir as a function of dose distributions are needed to design clinical trials aiming at the optimal sequencing, prescribed dose, and fractionation of radiation with immunotherapy (Gunderson and Young, 2018; Ko et al., 2018). The role of proton therapy in this context is extensively being studied (Lee et al., 2018; Tsuboi, 2018; Ebner et al., 2017; Fang et al., 2018).

The design of these clinical trials is challenging because of numerous potential combinations of systematic therapies, targeted therapies, immunotherapies, and radiation therapies. Furthermore, optimal combinations might depend on baseline patient characteristics, meaning that different immune

landscapes might require different therapeutic approaches to achieve the highest probability of immune activation. Testing all potential arms in clinical trials is nearly impossible so that bio-mathematical modeling is becoming more important to guide clinical trial design (Enderling et al., 2019).

Advances in Science and Technology to Meet Challenges

Precision medicine in radiation oncology aims at defining parameters to identify patients that will benefit in terms of tumor control or normal tissue toxicities from specific modalities, e.g. cancer cells harboring certain defects in the DNA damage response are susceptible to proton therapy (see secton on "Biomarkers"). Mechanisms have to be analyzed also in the context of multi-modality therapies.

Understanding the potential biological and immunological differences of proton therapy will reshape our understanding regarding the use of radiation therapy in general and proton therapy in particular. Based on immune response data from patients on clinical trials, we might develop novel plan optimization strategies to mitigate adverse immune-modulatory effects of radiation therapy. This requires assessment of patient specific immune response during and after RT, either via circulating biomarkers or advanced imaging techniques (Grassberger et al., 2019). This might ultimately lead to the establishment of personalized dose-volume constraints for immune structures and their inclusion in plan optimization. In this context proton therapy will have significant impact due to its dose-shaping capabilities combined with a low integral dose. These constraints and predictive models will also allow for identification of patients at high risk of severe RIL who may benefit from proton therapy. Especially when used together with drugs modulating the patient's immune response, a new planning paradigm might be required that takes the immune status of the patient into account, and ultimately treats the patient's lymphocyte reserve as a radiosensitive organ at risk requiring accurate dose calculation.

Concluding Remarks

Proton therapy does interact differently with systemic therapies compared to photon therapies due to the reduced integral dose. In cases where radiation and systemic drugs target similar damage or repair pathways treatment plans may have to be optimized for combined modality treatments considering interaction terms. One prime example is the lymphocyte depletion due to the dose bath outside of the target. We are just beginning to understand the impact of radiation therapy on the immune system and the potential of radiation therapy in combination with immune therapies. Additional research is needed to assess if proton therapy leads to enhanced systemic preservation of antitumor immunity or whether a low dose bath might even help to trigger immune responses under certain circumstances. Enhancing not only our physical and biological but also our immunological understanding of proton therapy is critical to guide patient selection and to enhance the clinical effectiveness of proton therapy in combination with checkpoint inhibitors and other approaches that interact with the immune system.

References

Agrawal MD, Pinho DF, Kulkarni NM, Hahn PF, Guimaraes AR, Sahani DV. Oncologic Applications of Dual-Energy CT in the Abdomen. Radiographics. 2014;34: 589–612.

Albertini F, Bolsi A, Lomax AJ, Rutz HP, Timmerman B, Goitein G 2008 Sensitivity of intensity modulated proton therapy plans to changes in patient weight. Radiother Oncol. 86 187-94

Albertini F, Matter M, Nenoff L, Zhang Y and Lomax A 2019 Online daily adaptive proton therapy Br J Radiol 20190594

Ang K K, Harris J, Wheeler R, Weber R, Rosenthal D I, Nguyen-Tân P F, Westra W H, Chung C H, Jordan R C, Lu C, Kim H, Axelrod R, Silverman C C, Redmond K P and Gillison M L 2010 Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer New England Journal of Medicine 363 24-35

Apolle R, Appold S, Bijl HP, Blanchard P, Bussink J, Faivre-Finn C, Khalifa J, Laprie A, Lievens Y, Madani I, Ruffier A, de Ruysscher D, van Elmpt W, Troost EGC 2019 Inter-observer variability in target delineation increases during adaptive treatment of head-and-neck and lung cancer. Acta Oncol. 10 1378-1385

Aznar MC, Girinsky T, Berthelsen AK, Aleman B, Beijert M, Hutchings M, Lievens Y, Meijnders P, Meidahl Petersen P, Schut D, Maraldo MV, van der Maazen R, Specht L 2017 Interobserver delineation uncertainty in involved-node radiation therapy (INRT) for early-stage Hodgkin lymphoma: on behalf of the Radiotherapy Committee of the EORTC lymphoma group. Acta Oncol. 56 608-613

Bangert M, Hennig P and Oelfke U 2013 Analytical probabilistic modeling for radiation therapy treatment planning Physics in medicine and biology 58 5401-19

Baumann BC, Mitra N, Harton JG, Xiao Y, Wojcieszynski AP, Gabriel PE, Zhong H, Geng H, Doucette A, Wei J, O'Dwyer PJ, Bekelman JE, Metz JM 2019 Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer. JAMA Oncol. 2020;6(2):237-246.

Beaton L, Bandula S, Gaze MN, Sharma RA. How rapid advances in imaging are defining the future of precision radiation oncology. Br J Cancer. 2019 Apr;120(8):779-790. doi: 10.1038/s41416-019-0412-y. Review.

Belosi M F, van der Meer R, Paz Garcia de Acilu Laa, Bolsi A, Weber D C, Lomax A J 2017 Treatment log files as a tool to identify treatment plan sensitivity to inaccuracies in scanned proton beam delivery. Radiotherapy and Oncology. 125-3, 514-519, ISSN 0167-8140, https://doi.org/10.1016/j.radonc.2017.09.037

Bennett GW, Archambeau JO, Archambeau BE, Meltzer JI, Wingate CL. Visualization and transport of positron emission from proton activation in vivo. Sci 1978; 200: 1151-3

Bernatowicz K, Geets X, Barragan A, Janssens G, Souris K, Sterpin E 2018. Feasibility of online IMPT adaptation using fast, automatic and robust dose restoration. Phys Med Biol. 63(8):085018. doi: 10.1088/1361-6560/aaba8c.

Bijman RG, Breedveld S, Arts T, Astreinidou E, de Jong MA, Granton PV, Petit SF, Hoogeman MS. Impact of model and dose uncertainty on model-based selection of oropharyngeal cancer patients for proton therapy. Acta Oncol. 2017 Nov;56(11):1444-1450.

Blanchard, P., A. J. Wong, G. B. Gunn, A. S. Garden, A. S. R. Mohamed, D. I. Rosenthal, J. Crutison, R. Wu, X. Zhang, X. R. Zhu, R. Mohan, M. V. Amin, C. D. Fuller and S. J. Frank (2016). "Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort." Radiother Oncol 121(3): 381-386.

Boria AJ, Pirlepesov F, Stuckey JC, Axente M, Gargone MA, Hua CH. 2018. Interplay Effect of Target Motion and Pencil-Beam Scanning in Proton Therapy for Pediatric Patients. Int J Part Ther. 2018, Fall;5(2):1-10. https://doi.org/10.14338/IJPT-17-00030.1.

Botas P, Kim J, Winey B, Paganetti H. 2018 Online adaption approaches for intensity modulated proton

therapy for head and neck patients based on cone beam CTs and Monte Carlo simulations. Phys Med Biol. 64 :015004. doi: 10.1088/1361-6560/aaf30b.

Bright S J, Flint D B, Chakraborty S, McFadden C H, Yoon D S, Bronk L, Titt U, Mohan R, Grosshans D R, Sumazin P, Shaitelman S F, Asaithamby A and Sawakuchi G O 2019 Non-homologous end joining is more important than proton linear energy transfer in dictating cell death Int J Radiat Oncol Biol Phys In Press

Brouwer CL, Steenbakkers RJ, Bourhis J, Budach W, Grau C, Grégoire V, van Herk M, Lee A, Maingon P, Nutting C, O'Sullivan B, Porceddu SV, Rosenthal DI, Sijtsema NM, Langendijk JA. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol. 2015 Oct;117(1):83-90

Buitenhuis HJT, Diblen F, Brzezinski KW, Brandenburg S, Dendooven P, Beam-on imaging of short-lived positron emitters during proton therapy, Phys Med Biol. 2017; 62:4654-4672

Cao W, Lim G, Liao L, Li Y, Jiang S, Li X, Li H, Suzuki K, Zhu XR, Gomez D, Zhang X. 2014. Proton energy optimization and reduction for intensity-modulated proton therapy. Phys Med Biol. 2014, Nov 7;59(21):6341-54. https://doi.org/10.1088/0031-9155/59/21/6341.

Chaikh, A., V. Calugaru, P. Y. Bondiau, J. Thariat and J. Balosso (2018). "Impact of the NTCP modeling on medical decision to select eligible patient for proton therapy: the usefulness of EUD as an indicator to rank modern photon vs proton treatment plans." Int J Radiat Biol: 1-9.

Chan A W and Liebsch N J 2008 Proton radiation therapy for head and neck cancer J Surg Oncol 97 697-700

Chang JY, Zhang X, Knopf A, Li H, Mori S, Dong L, Lu HM, Liu W, Badiyan SN, Both S, Meijers A, Lin L, Flampouri S, Li Z, Umegaki K, Simone CB 2nd, Zhu XR. Consensus Guidelines for Implementing Pencil-Beam Scanning Proton Therapy for Thoracic Malignancies on Behalf of the PTCOG Thoracic and Lymphoma Subcommittee. Int J Radiat Oncol Biol Phys. 2017 Sep 1;99(1):41-50. doi: 10.1016/j.ijrobp.2017.05.014.

Chen, Y., C. Grassberger, J. Li, T. S. Hong and H. Paganetti (2018). "Impact of potentially variable RBE in liver proton therapy." Phys Med Biol 63(19): 195001.

Corradini S, Alongi F, Andratschke N, Belka C, Boldrini L, Cellini F, Debus J, Guckenberger M, Hörner-Rieber J, Lagerwaard FJ, Mazzola R, Palacios MA, Philippens MEP, Raaijmakers CPJ, Terhaard CHJ, Valentini V, Niyazi M. MR-guidance in clinical reality: current treatment challenges and future perspectives. Radiat Oncol. 2019 Jun 3;14(1):92. doi: 10.1186/s13014-019-1308-y. Review.

Crocenzi T, Cottam B, Newell P, Wolf R F, Hansen P D, Hammill C, Solhjem M C, To Y Y, Greathouse A, Tormoen G, Jutric Z, Young K, Bahjat K S, Gough M J and Crittenden M R 2016 A hypofractionated radiation regimen avoids the lymphopenia associated with neoadjuvant chemoradiation therapy of borderline resectable and locally advanced pancreatic adenocarcinoma J Immunother Cancer 4 45

Cubillos-Mesías M, Troost EGC, Lohaus F, Agolli L, Rehm M, Richter C, Stützer K. 2019 Including anatomical variations in robust optimization for head and neck proton therapy can reduce the need of adaptation. Radiother Oncol. 131 127-134.

Cummings D, Tang S, Ichter W, Wang P, Sturgeon JD, Lee AK, Chang C. Four-dimensional Plan Optimization for the Treatment of Lung Tumors Using Pencil-beam Scanning Proton Radiotherapy. Cureus. 2018 Aug 23;10(8):e3192. doi: 10.7759/cureus.3192.

Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013 Mar 14;368(11):987-98.

Das IJ, McGee KP, Tyagi N, Wang H. Role and future of MRI in radiation oncology. Br J Radiol. 2019;92: 20180505.

Davuluri R, Jiang W, Fang P, Xu C, Komaki R, Gomez D R, Welsh J, Cox J D, Crane C H, Hsu C C and Lin S H 2017 Lymphocyte Nadir and Esophageal Cancer Survival Outcomes After Chemoradiation Therapy Int J Radiat Oncol Biol Phys 99 128-35

Deffet S, Macq B, Righetto R, Vander Stappen F and Farace P 2017 Registration of pencil beam proton radiography data with X-ray CT Med Phys 44 5393-401

Degiovanni and Amaldi U: Proton and Carbon Linacs for Hadron Therapy, Proceedings of LINAC2014, ISBN 978-3-95450-142-7, Geneva, Switzerland FRIOB02, (2014) 1207-1212

Delaney AR, Dahele M, Tol JP, Kuijper IT, Slotman BJ, Verbakel WFAR. Using a knowledge-based planning solution to select patients for proton therapy. Radiother Oncol. 2017 Aug;124(2):263-270.

Durante, M., H. Paganetti, A. Pompos, S. F. Kry, X. Wu and D. R. Grosshans (2019). "Report of a National Cancer Institute special panel: Characterization of the physical parameters of particle beams for biological research." Med Phys 46(2): e37-e52.

Ebner D K, Tinganelli W, Helm A, Bisio A, Yamada S, Kamada T, Shimokawa T and Durante M 2017 The Immunoregulatory Potential of Particle Radiation in Cancer Therapy Frontiers in immunology 8 99

El Naqa, I., J. Bradley, A. I. Blanco, P. E. Lindsay, M. Vicic, A. Hope and J. O. Deasy (2006). "Multivariable modeling of radiotherapy outcomes, including dose-volume and clinical factors." Int J Radiat Oncol Biol Phys 64(4): 1275-1286.

El Naqa, I., S. L. Kerns, J. Coates, Y. Luo, C. Speers, C. M. L. West, B. S. Rosenstein and R. K. Ten Haken (2017). "Radiogenomics and radiotherapy response modeling." Phys Med Biol 62(16): R179-R206.

Elhalawani H, Lin T A, Volpe S, Mohamed A S R, White A L, Zafereo J, Wong A J, Berends J E, AboHashem S, Williams B, Aymard J M, Kanwar A, Perni S, Rock C D, Cooksey L, Campbell S, Yang P, Nguyen K, Ger R B, Cardenas C E, Fave X J, Sansone C, Piantadosi G, Marrone S, Liu R, Huang C, Yu K, Li T, Yu Y, Zhang Y, Zhu H, Morris J S, Baladandayuthapani V, Shumway J W, Ghosh A, Pohlmann A, Phoulady H A, Goyal V, Canahuate G, Marai G E, Vock D, Lai S Y, Mackin D S, Court L E, Freymann J, Farahani K, Kaplathy-Cramer J and Fuller C D 2018 Machine Learning Applications in Head and Neck Radiation Oncology: Lessons From Open-Source Radiomics Challenges Front Oncol. 8:294. 10.3389/fonc.2018.00294. eCollection 2018.

Ellsworth S G 2018 Field size effects on the risk and severity of treatment-induced lymphopenia in patients undergoing radiation therapy for solid tumors Adv Radiat Oncol 3 512-9

Enderling H, Alfonso J C L, Moros E, Caudell J J and Harrison L B 2019 Integrating Mathematical Modeling into the Roadmap for Personalized Adaptive Radiation Therapy Trends Cancer 5 467-74

Engelsman M, Schwarz M and Dong L 2013 Physics Controversies in Proton Therapy Seminars in Radiation Oncology 23 88-96

Engwall E, Fredriksson A, Glimelius L. 4D robust optimization including uncertainties in time structures can reduce the interplay effect in proton pencil beam scanning radiation therapy. Med Phys. 2018 Jul 16.

doi: 10.1002/mp.13094.

Eulitz, J., E. G. C. Troost, F. Raschke, E. Schulz, B. Lutz, A. Dutz, S. Lock, P. Wohlfahrt, W. Enghardt, C. Karpowitz, M. Krause and A. Luhr (2019). "Predicting late magnetic resonance image changes in glioma patients after proton therapy." Acta Oncol: 1-4.

Fager, M., I. Toma-Dasu, M. Kirk, D. Dolney, E. S. Diffenderfer, N. Vapiwala and A. Carabe (2015). "Linear energy transfer painting with proton therapy: a means of reducing radiation doses with equivalent clinical effectiveness." Int J Radiat Oncol Biol Phys 91(5): 1057-1064.

Fang P, Shiraishi Y, Verma V, Jiang W, Song J, Hobbs B P and Lin S H 2018 Lymphocyte-Sparing Effect of Proton Therapy in Patients with Esophageal Cancer Treated with Definitive Chemoradiation Int J Part Ther 4 23-32

Fay, M., A. Tan, R. Fisher, M. Mac Manus, A. Wirth and D. Ball (2005). "Dose-volume histogram analysis as predictor of radiation pneumonitis in primary lung cancer patients treated with radiotherapy." Int J Radiat Oncol Biol Phys 61(5): 1355-1363.

Ferrero V, Fiorina E, Morrocchi M, Pennazio F, Baroni G, Battistoni G, Belcari N, Camarlinghi N, Ciocca M, Del Guerra A, Donetti M, Giordanengo S, Giraudo G, Patera V, Peroni C, Rivetti A, Rolo MDDR, Rossi S, Rosso V, Sportelli G, Tampellini S, Valvo F, Wheadon R, Cerello P, Bisogni MG, Online proton therapy monitoring: clinical test of a Silicon-photodetector-based in-beam PET, Sci Rep. 2018; 8:4100

Fiorina E, Ferrero V, Pennazio F, Baroni G, Battistoni G, Belcari N, Cerello P, Camarlinghi N, Ciocca M, Del Guerra A, Donetti M, Ferrari A, Giordanengo S, Giraudo G, Mairani A, Morrocchi M, Peroni C, Rivetti A, Da Rocha Rolo MD, Rossi S, Rosso V, Sala P, Sportelli G, Tampellini S, Valvo F, Wheadon R, Bisogni MG, Monte Carlo simulation tool for online treatment monitoring in hadrontherapy with in-beam PET: A patient study, Phys Med. 2018; 51:71–80

Fracchiolla F, Fellin F, Innocenzi M, Lipparini M, Lorentini S, Widesott L, Farace P, Schwarz M. A pre-absorber optimization technique for pencil beam scanning proton therapy treatments. Med. Phys 2019 Jan;57:145-152.

Fredriksson A 2012 A characterization of robust radiation therapy treatment planning methods-from expected value to worst case optimization Medical physics 39 5169-81

Fredriksson A, Forsgren A and Hardemark B 2011 Minimax optimization for handling range and setup uncertainties in proton therapy Medical physics 38 1672-84

Ge S, Wang X, Liao Z, Zhang L, Sahoo N, Yang J, Guan F, Mohan R. Potential for Improvements in Robustness and Optimality of Intensity-Modulated Proton Therapy for Lung Cancer with 4-Dimensional Robust Optimization. Cancers (Basel). 2019 Jan 1;11(1). pii: E35. doi: 10.3390/cancers11010035.

Gelover E, Deisher AJ, Herman MG, Johnson JE, Kruse JJ, Tryggestad EJ. 2019. Clinical implementation of respiratory-gated spot-scanning proton therapy: An efficiency analysis of active motion management. J Appl Clin Med Phys. 2019, May;20(5):99-108. https://doi.org/10.1002/acm2.12584.

Gerbershagen A., Meer D., Schippers JM, Seidel M., A novel beam optics concept in a particle therapy gantry utilizing the advantages of superconducting magnets., Z Med Phys 2016, 26(3):224-37

Giraud P, Gasnier A, El Ayachy R, Kreps S, Foy JP, Durdux C, Huguet F, Burgun A, Bibault JE 2019 Radiomics and Machine Learning for Radiotherapy in Head and Neck Cancers. Front Oncol. 2019 9:174. doi: 10.3389/fonc.2019.00174. eCollection 2019.

Gomez D R and Chang J Y 2011 Adaptive radiation for lung cancer J Oncol 2011

Gora J, Kuess P, Stock M, Andrzejewski P, Knausl B, Paskeviciute B, Altorjai G and Georg D 2015 ART for head and neck patients: On the difference between VMAT and IMPT Acta Oncol 54 1166-74

Graeff C, Constantinescu A, Lüchtenborg R, Durante M, Bert C. Multigating, a 4D optimized beam tracking in scanned ion beam therapy. Technol Cancer Res Treat. 2014 Dec;13(6):497-504. doi: 10.7785/tcrtexpress.2013.600277.

Grassberger C, Dowdell S, Lomax A, Sharp G, Shackleford J, Choi N, Willers H, Paganetti H. 2013 Motion interplay as a function of patient parameters and spot size in spot scanning proton therapy for lung cancer. Int J Radiat Oncol Biol Phys. 86 380-6.

Grassberger C, Geng C, McClatchy III D, Kamran S C, Fintelmann F, Maruvka Y E, Piotrowska Z, Willers H, Sequist L V, Hata A and Paganetti H 2019 Patient-specific tumor growth trajectories determine persistent and resistant cancer cell populations during treatment with targeted therapies Cancer Research 79 3776-88

Grassberger, C., A. Trofimov, A. Lomax and H. Paganetti (2011). "Variations in linear energy transfer within clinical proton therapy fields and the potential for biological treatment planning." Int J Radiat Oncol Biol Phys 80(5): 1559-1566.

Grevillot L, Stock M, Vatnitsky S. 2015. Evaluation of beam delivery and ripple filter design for non-isocentric proton and carbon ion therapy. Phys Med Biol. 2015, Oct 21;60(20):7985-8005. https://doi.org/10.1088/0031-9155/60/20/7985.

Grosse, N., A. O. Fontana, E. B. Hug, A. Lomax, A. Coray, M. Augsburger, H. Paganetti, A. A. Sartori and M. Pruschy (2014). "Deficiency in homologous recombination renders Mammalian cells more sensitive to proton versus photon irradiation." Int J Radiat Oncol Biol Phys 88(1): 175-181.

Guerreiro F, Koivula L, Seravalli E, Janssens GO, Maduro JH, Brouwer CL, Korevaar EW, Knopf AC, Korhonen J, Raaymakers BW. Feasibility of MRI-only photon and proton dose calculations for pediatric patients with abdominal tumors. Phys Med Biol. 2019 Feb 25;64(5):055010. doi: 10.1088/1361-6560/ab0095.

Gunderson A J and Young K H 2018 Exploring optimal sequencing of radiation and immunotherapy combinations Adv Radiat Oncol 3 494-505

Gustafson M P, Bornschlegl S, Park S S, Gastineau D A, Roberts L R, Dietz A B and Hallemeier C L 2017 Comprehensive assessment of circulating immune cell populations in response to stereotactic body radiation therapy in patients with liver cancer Adv Radiat Oncol 2 540-7

Haas-Kogan, D., D. Indelicato, H. Paganetti, N. Esiashvili, A. Mahajan, T. Yock, S. Flampouri, S. MacDonald, M. Fouladi, K. Stephen, J. Kalapurakal, S. Terezakis, H. Kooy, D. Grosshans, M. Makrigiorgos, K. Mishra, T. Y. Poussaint, K. Cohen, T. Fitzgerald, V. Gondi, A. Liu, J. Michalski, D. Mirkovic, R. Mohan, S. Perkins, K. Wong, B. Vikram, J. Buchsbaum and L. Kun (2018). "National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury." Int J Radiat Oncol Biol Phys 101(1): 152-168.

Hammi A, Koenig S, Weber DC, Poppe B, Lomax AJ. 2018 Patient positioning verification for proton therapy using proton radiography. Phys Med Biol. Dec 10;63(24):245009.

Han, P., P. Lakshminarayanan, W. Jiang, I. Shpitser, X. Hui, S. H. Lee, Z. Cheng, Y. Guo, R. H. Taylor, S. A. Siddiqui, M. Bowers, K. Sheikh, A. Kiess, B. R. Page, J. Lee, H. Quon and T. R. McNutt (2019). "Dose/Volume histogram patterns in Salivary Gland subvolumes influence xerostomia injury and

recovery." Sci Rep 9(1): 3616.

Heinrich MP, Simpson IJ, Papież BW, Brady SM, Schnabel JA 2016. Deformable image registration by combining uncertainty estimates from supervoxel belief propagation. Med Image Anal 27 57-71.

Henke LE, Contreras JA, Green OL, Cai B, Kim H, Roach MC, Olsen JR, Fischer-Valuck B, Mullen DF, Kashani R, Thomas MA, Huang J, Zoberi I, Yang D, Rodriguez V, Bradley JD, Robinson CG, Parikh P, Mutic S, Michalski J. 2018 Magnetic Resonance Image-Guided Radiotherapy (MRIgRT): A 4.5-Year Clinical Experience. Clin Oncol (R Coll Radiol). Nov;30(11):720-727.

Hiramoto K, Umezawa M et al., The synchrotron and its related technology for ion beam therapy, Nucl. Instr. Meth. B 261 (2007) 786–790.

Hoesl M, Deepak S, Moteabbed M, Jassens G, Orban J, Park Y K, Parodi K, Bentefour E H and Lu H M 2016 Clinical commissioning of an in vivo range verification system for prostate cancer treatment with anterior and anterior oblique proton beams Phys Med Biol 61 3049-62

Hoffmann L, Alber M, Jensen M F, Holt M I and Moller D S 2017 Adaptation is mandatory for intensity modulated proton therapy of advanced lung cancer to ensure target coverage Radiother Oncol 122 400-5

Hori C, Aoki T, Seki T 2019 Variable-energy isochronous accelerator with cotangential orbits for proton beam therapy. Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment. 922, pp 352-356, ISSN 0168-9002, https://doi.org/10.1016/j.nima.2019.01.005

Hope, A. J., P. E. Lindsay, I. El Naqa, J. R. Alaly, M. Vicic, J. D. Bradley and J. O. Deasy (2006). "Modeling radiation pneumonitis risk with clinical, dosimetric, and spatial parameters." Int J Radiat Oncol Biol Phys 65(1): 112-124.

Horst F, Adi W, Aricò G, Brinkmann KT, Durante M, Reidel CA, Rovituso M, Weber U, Zaunick HG, Zink K, Schuy C, Measurement of PET isotope production cross sections for protons and carbon ions on carbon and oxygen targets for applications in particle therapy range verification, Phys Med Biol. 2019; 64:205012

Hsi WC, Moyers MF, Nichiporov D, Anferov V, Wolanski M, Allgower CE, Farr JB, Mascia AE, Schreuder AN. 2009. Energy spectrum control for modulated proton beams. Med Phys. 2009, Jun;36(6):2297-308. https://doi.org/10.1118/1.3132422.

Hueso-González F, Fiedler F, Golnik C, Kormoll T, Pausch G, Petzoldt J, Römer KE, Enghardt W. 2016 Compton Camera and Prompt Gamma Ray Timing: Two Methods for In Vivo Range Assessment in Proton Therapy. Front Oncol. Apr 12;6:80

Hueso-Gonzalez F, Rabe M, Ruggieri T A, Bortfeld T and Verburg J M 2018 A full-scale clinical prototype for proton range verification using prompt gamma-ray spectroscopy Phys Med Biol 63 185019

Hunt A, Hansen VN, Oelfke U, Nill S, Hafeez S. Adaptive Radiotherapy Enabled by MRI Guidance. Clin Oncol (R Coll Radiol). 2018 Nov;30(11):711-719. doi: 10.1016/j.clon.2018.08.001.

Hwang, W. L., Niemierko, A., Hwang, K. L., Hubbeling, H., Schapira, E., Gainor, J. F., & Keane, F. K. Clinical Outcomes in Patients With Metastatic Lung Cancer Treated With PD-1/PD-L1 Inhibitors and Thoracic Radiotherapy. JAMA Oncology 2018, 4(2), 253.

IBA Website 2019: https://iba-worldwide.com/proton-therapy/proton-therapy-solutions/proteus-one

Ibragimov, B., D. A. S. Toesca, D. T. Chang, Y. Yuan, A. C. Koong, L. Xing and I. R. Vogelius (2020).

"Deep learning for identification of critical regions associated with toxicities after liver stereotactic body radiation therapy." Med Phys.

Ibragimov, B., D. A. S. Toesca, Y. Yuan, A. C. Koong, D. T. Chang and L. Xing (2019). "Neural Networks for Deep Radiotherapy Dose Analysis and Prediction of Liver SBRT Outcomes." IEEE J Biomed Health Inform 23(5): 1821-1833.

Indelicato, D. J., S. Flampouri, R. L. Rotondo, J. A. Bradley, C. G. Morris, P. R. Aldana, E. Sandler and N. P. Mendenhall (2014). "Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy." Acta Oncol 53(10): 1298-1304.

Indelicato DJ, Rotondo RL, Uezono H, Sandler ES, Aldana PR, Ranalli NJ, Beier AD, Morris CG, Bradley JA. Outcomes Following Proton Therapy for Pediatric Low-Grade Glioma. Int J Radiat Oncol Biol Phys 2019 104(1):149-156.

Inoue T, Widder J, van Dijk LV, Takegawa H, Koizumi M, Takashina M, Usui K, Kurokawa C, Sugimoto S, Saito AI, Sasai K, Van't Veld AA, Langendijk JA, Korevaar EW. Limited Impact of Setup and Range Uncertainties, Breathing Motion, and Interplay Effects in Robustly Optimized Intensity Modulated Proton Therapy for Stage III Non-small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2016 Nov 1;96(3):661-9. doi: 1,210.1016/j.ijrobp.2016.06.2454.

Iwata, Furukawa T, Mizushima K et al., Multiple-Eenergy operation with quasi-DC extension of flattops at HIMAC WITH QUASI-DC EXTENSION OF. Proceedings of IPAC'10, Kyoto, Japan. 2010, MOPEA008, 79-81 http://accelconf.web.cern.ch/AccelConf/IPAC10/papers/mopea008.pdf.

Jaffray DA, Drake DG, Moreau M, Martinez AA, Wong JW. 1999 A radiographic and tomographic imaging system integrated into a medical linear accelerator for localization of bone and soft-tissue targets. Int J Radiat Oncol Biol Phys. Oct 1;45(3):773-89.

Jagt T, Breedveld S, van de Water S, Heijmen B and Hoogeman M. 2017 Near real-time automated dose restoration in IMPT to compensate for daily tissue density variations in prostate cancer. Phys. Med. Biol. 62 4254–4272. https://doi.org/10.1088/1361-6560/aa5c12

Jason K. Molitoris, Tejan Diwanji, James W. Snider III, Sina Mossahebi, Santanu Samanta, Shahed N. Badiyan, Charles B. Simone II, Pranshu Mohindra. Advances in the use of motion management and image guidance in radiation therapy treatment for lung cancer. J Thorac Dis 2018;10(Suppl 21):S2437-S2450.

Jensen G L, Blanchard P, Gunn G B, Garden A S, Fuller C D, Sturgis E M, Gillison M L, Phan J, Morrison W H, Rosenthal D I and Frank S J 2017 Prognostic impact of leukocyte counts before and during radiotherapy for oropharyngeal cancer Clinical and Translational Radiation Oncology 7 28-35

Johnson J, Beltran C, Tseung H, Mundy D, Kruse J, Whitaker T, Herman, M., Furutani, K 2019 Highly efficient and sensitive patient-specific quality assurance for spot-scanned proton therapy. PLOS ONE. 14. e0212412. https://doi.org/10.1371/journal.pone.0212412

Johnson RP. Review of medical radiography and tomography with proton beams. Rep Prog Phys. 2018;81: 016701.

Kainz W, Neufeld E, Bolch WE, Graff CG, Kim CH, Kuster N, Lloyd B, Morrison T, Segars P, Yeom YS, Zankl M, Xu XG, Tsui BMW 2019 Advances in Computational Human Phantoms and Their Applications in Biomedical Engineering - A Topical Review. IEEE Trans Radiat Plasma Med Sci. Jan;3(1):1-23. doi: 10.1109/TRPMS.2018.2883437.

Kalbasi A, June C H, Haas N and Vapiwala N 2013 Radiation and immunotherapy: a synergistic

combination The Journal of clinical investigation 123 2756-63

Kamran SC, Goldberg SI, Kuhlthau KA, Lawell MP, Weyman EA, Gallotto SL, Hess CB, Huang MS, Friedmann AM, Abrams AN, MacDonald SM, Pulsifer MB, Tarbell NJ, Ebb DH, Yock TI. Quality of life in patients with proton-treated pediatric medulloblastoma: Results of a prospective assessment with 5-year follow-up. Cancer 2018 124, Issue16, 3390-3400

Kang JH, Wilkens JJ, Oelfke U. 2008. Non-uniform depth scanning for proton therapy systems employing active energy variation. Phys Med Biol. 2008, May 7;53(9):N149-55. https://doi.org/10.1088/0031-9155/53/9/N01.

Kang M, Chen H, Cessac R, Pang D. 2018. Commissioning of a Unique Penumbra Sharpening Adaptive Aperture. Int J Part Ther. 2018, Sep Vol. 5, No. 2, p80.

Kaur P and Asea A 2012 Radiation-induced effects and the immune system in cancer Frontiers in oncology 2 191

Kida S, Nakamoto T, Nakano M, Nawa K, Haga A, Kotoku J, Yamashita H, Nakagawa K. Cone Beam Computed Tomography Image Quality Improvement Using a Deep Convolutional Neural Network. Cureus. 2018 Apr 29;10(4):e2548. doi: 10.7759/cureus.2548.

Kierkels RGJ, Fredriksson A, Both S, Langendijk JA, Scandurra D, Korevaar EW. Automated Robust Proton Planning Using Dose-Volume Histogram-Based Mimicking of the Photon Reference Dose and Reducing Organ at Risk Dose Optimization. Int J Radiat Oncol Biol Phys. 2019 Jan 1;103(1):251-258.

Klimpki G, Psoroulas S, Bula C, Rechsteiner U, Eichin M, Weber DC, Lomax A, Meer D. 2017. A beam monitoring and validation system for continuous line scanning in proton therapy. Phys Med Biol. 2017, Jul 12;62(15):6126-6143. https://doi.org/10.1088/1361-6560/aa772e.

Klimpki G, Zhang Y, Fattori G, Psoroulas S, Weber DC, Lomax A, Meer D. 2018. The impact of pencil beam scanning techniques on the effectiveness and efficiency of rescanning moving targets. Phys Med Biol. 2018, Jul 11;63(14) https://doi.org/10.1088/1361-6560/aacd27.

Knopf AC, Lomax A. 2013 In vivo proton range verification: a review. Phys Med Biol. Aug 7;58(15):R131-60

Ko E C, Benjamin K T and Formenti S C 2018 Generating antitumor immunity by targeted radiation therapy: Role of dose and fractionation Adv Radiat Oncol 3 486-93

Kobashi, K., A. Prayongrat, T. Kimoto, C. Toramatsu, Y. Dekura, N. Katoh, S. Shimizu, Y. M. Ito and H. Shirato (2018). "Assessing the uncertainty in a normal tissue complication probability difference (NTCP): radiation-induced liver disease (RILD) in liver tumour patients treated with proton vs X-ray therapy." J Radiat Res 59(suppl_1): i50-i57.

Koehler AM, Schneider RJ, Sisterson JM. Flattening of proton dose distributions for large-field radiotherapy. Med Phys. 1977; 4:297–301. [PubMed: 407436]

Koehler AM, LBL Pub #22962, (1987)

Konings K, Vandevoorde C, Baselet B, Baatout S, Moreels M. Combination Therapy With Charged Particles and Molecular Targeting: A Promising Avenue to Overcome Radioresistance. Front Oncol. 2020; 10: 128.

Kontaxis C, Bol GH, Lagendijk JJ, Raaymakers BW.2015 A new methodology for inter- and intrafraction plan adaptation for the MR-linac. Phys Med Biol. Oct 7;60(19):7485-97

Korevaar E W, Habraken S J M, Scandurra D, Kierkels R G J, Unipan M, Eenink M G C, Steenbakkers

R, Peeters S G, Zindler J D, Hoogeman M and Langendijk J A 2019 Practical robustness evaluation in radiotherapy - A photon and proton-proof alternative to PTV-based plan evaluation Radiother Oncol 141 267-74

Krimmer J, Dauvergne D, Létang JM, Testa É. Prompt-gamma monitoring in hadrontherapy: a review. Nucl Instrum Methods A 2018; 878: 58–73

Kurz C, Maspero M, Savenije M H F, Landry G, Kamp F, Pinto M, Li M, Parodi K, Belka C and van den Berg C A T 2019 CBCT correction using a cycle-consistent generative adversarial network and unpaired training to enable photon and proton dose calculation Phys Med Biol 64 225004

Landry G, Hua CH. Current state and future applications of radiological image guidance for particle therapy. Med Phys. 2018 Nov;45(11):e1086-e1095. doi: 10.1002/mp.12744. Review.

Lang C, Habs D, Parodi K, Thirolf PG, Sub-millimeter nuclear medical imaging with high sensitivity in positron emission tomography using β+γ coincidences, J Instrum 2014; 9: P01008

Langendijk JA, Boersma LJ, Rasch CRN, van Vulpen M, Reitsma JB, van der Schaaf A, Schuit E. Clinical Trial Strategies to Compare Protons With Photons. Semin Radiat Oncol. 2018 Apr;28(2):79-87. Review.

Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol. 2013 Jun;107(3):267-73

Lecoq P, Morel C, Prior J et al, Roadmap toward the 10 ps time-of-flight PET challenge, Phys Med Biol 2020

Lee H J, Jr., Zeng J and Rengan R 2018 Proton beam therapy and immunotherapy: an emerging partnership for immune activation in non-small cell lung cancer Transl Lung Cancer Res 7 180-8

Lee M, Wynne C, Webb S, Nahum A E and Dearnaley D 1994 A comparison of proton and megavoltage X-ray treatment planning for prostate cancer Radiotherapy and Oncology 33 239-53

Lee, T. F., P. J. Chao, H. M. Ting, L. Chang, Y. J. Huang, J. M. Wu, H. Y. Wang, M. F. Horng, C. M. Chang, J. H. Lan, Y. Y. Huang, F. M. Fang and S. W. Leung (2014). "Using multivariate regression model with least absolute shrinkage and selection operator (LASSO) to predict the incidence of Xerostomia after intensity-modulated radiotherapy for head and neck cancer." PLoS One 9(2): e89700.

Li H, Li Y, Zhang X, Li X, Liu W, Gillin M T and Zhu X R 2012 Dynamically accumulated dose and 4D accumulated dose for moving tumors Med Phys 39 7359-67

Li H, Zhu X R and Zhang X 2015 Reducing Dose Uncertainty for Spot-Scanning Proton Beam Therapy of Moving Tumors by Optimizing the Spot Delivery Sequence Int J Radiat Oncol Biol Phys 93 547-56

Li X, Liu G, Janssens G, De Wilde O, Bossier V, Lerot X, Pouppez A, Yan D, Stevens C, Kabolizadeh P, Ding X. 2019. The first prototype of spot-scanning proton arc treatment delivery. Radiother Oncol. 2019, Aug;137:130-136. https://doi.org/10.1016/j.radonc.2019.04.032.

Li, Y., M. Dykstra, T. D. Best, J. Pursley, N. Chopra, F. K. Keane, M. J. Khandekar, G. C. Sharp, H. Paganetti, H. Willers, F. J. Fintelmann and C. Grassberger (2019). "Differential inflammatory response dynamics in normal lung following stereotactic body radiation therapy with protons versus photons." Radiotherapy and Oncology 136: 169-175.

Liao Z X, Lee J J, Komaki R, Gomez D, O'Reilly M and Allen P 2016 Bayesian randomized trial comparing intensity modulated radiation therapy versus passively scattered proton therapy for locally

advanced non-small cell lung cancer. Journal of Clinical Oncology 34 8500

Liu CC, Huang HM 2020 A Deep Learning Approach for Converting Prompt Gamma Images to Proton Dose Distributions: A Monte Carlo Simulation Study Phys Med 69 110

Liu, Q., P. Ghosh, N. Magpayo, M. Testa, S. Tang, L. Gheorghiu, P. Biggs, H. Paganetti, J. A. Efstathiou, H. M. Lu, K. D. Held and H. Willers (2015). "Lung cancer cell line screen links fanconi anemia/BRCA pathway defects to increased relative biological effectiveness of proton radiation." Int J Radiat Oncol Biol Phys 91(5): 1081-1089.

Liu R, Xiong S, Zhang L and Chu Y 2010 Enhancement of antitumor immunity by low-dose total body irradiationis associated with selectively decreasing the proportion and number of T regulatory cells Cell Mol Immunol 7 157-62

Liu W, Schild S E, Chang J Y, Liao Z, Chang Y H, Wen Z, Shen J, Stoker J B, Ding X, Hu Y, Sahoo N, Herman M G, Vargas C, Keole S, Wong W and Bues M 2016 Exploratory Study of 4D versus 3D Robust Optimization in Intensity Modulated Proton Therapy for Lung Cancer Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):523-33. doi: 10.1016/j.ijrobp.2015.11.002.

Lomax, A. (1999). "Intensity modulation methods for proton radiotherapy." Physics in Medicine and Biology 44: 185-205.

Lomax A 2018 What will the medical physics of proton therapy look like 10 yr from now? A personal view. Med Phys. Nov;45(11):e984-e993

Lomax A J, Bortfeld T, Goitein G, Debus J, Dykstra C, Tercier P-A, Coucke P A and Mirimanoff R O 1999 A treatment planning inter-comparison of proton and intensity modulated photon radiotherapy Radiotherapy and Oncology 51 257-71

Ma J, Wan Chan Tseung HS, Herman MG, Beltran C 2018. A robust intensity modulated proton therapy optimizer based on Monte Carlo dose calculation. Med Phys Jul 18. doi: 10.1002/mp.13096.

MacKay RI 2018 Image Guidance for Proton Therapy. Clin Oncol (R Coll Radiol). May;30(5):293-298

Manem V S K, Lambie M, Smith I, Smirnov P, Kofia V, Freeman M, Koritzinsky M, Abazeed M E, Haibe-Kains B and Bratman S V 2019 Modeling cellular response in large-scale radiogenomic databases to advance precision radiotherapy Cancer research canres.0179.2019

Marchant TE, Joshi KD, Moore CJ. 2018 Accuracy of radiotherapy dose calculations based on cone-beam CT: comparison of deformable registration and image correction based methods. Phys Med Biol. 2018 Mar 12;63(6):065003

Marks, L. B., S. M. Bentzen, J. O. Deasy, F. M. Kong, J. D. Bradley, I. S. Vogelius, I. El Naqa, J. L. Hubbs, J. V. Lebesque, R. D. Timmerman, M. K. Martel and A. Jackson (2010). "Radiation dose-volume effects in the lung." Int J Radiat Oncol Biol Phys 76(3 Suppl): S70-76.

Martins PG, Dal Bello R, Ackermann B, Brons S, Hermann G, Kihm T, Seco J 2020 PIBS: Proton and Ion Beam Spectroscopy for in Vivo Measurements of Oxygen, Carbon, and Calcium Concentrations in the Human Body Sci Rep10 7007

Maspero M, van den Berg CAT, Landry G, Belka C, Parodi K, Seevinck PR, Raaymakers BW, Kurz C. Feasibility of MR-only proton dose calculations for prostate cancer radiotherapy using a commercial pseudo-CT generation method. Phys Med Biol. 2017 Nov 21;62(24):9159-9176. doi: 10.1088/1361-6560/aa9677.

Masuda T, Nishio T, Kataoka J, Arimoto M, Sano A, Karasawa K, ML-EM algorithm for dose estimation

using PET in proton therapy, Phys Med Biol 2019; 64: 175011

Matter M, Nenoff L, Meier G, Weber DC, Lomax AJ, Albertini F. Alternatives to patient specific verification measurements in proton therapy: a comparative experimental study with intentional errors. Phys Med Biol. 2018 Oct 17;63(20):205014. doi: 10.1088/1361-6560/aae2f4.

Matter M, Nenoff L, Meier G, Weber D C, Lomax A J and Albertini F 2019 Intensity modulated proton therapy plan generation in under ten seconds Acta Oncol 58 1435-9

Matter M, Nenoff L, Marc L, Weber DC, Lomax AJ, Albertini 2020 Update on yesterday's dose - use of delivery log-files for daily adaptive proton therapy (DAPT) Phys Med Biol. doi: 10.1088/1361-6560/ab9f5e.

Mazal A, Prezado Y, Ares C, de Marzi L, Patriarca A, Miralbell R, Favaudon V 2020 FLASH and minibeams in radiation therapy: the effect of microstructures on time and space and their potential application to protontherapy. Br J Radiol. 20190807. doi: 10.1259/bjr.20190807.

McNamara, A. L., J. Schuemann and H. Paganetti (2015). "A phenomenological relative biological effectiveness (RBE) model for proton therapy based on all published in vitro cell survival data." Phys Med Biol 60(21): 8399-8416.

Meier G, Leiser D, Besson R, Mayor A, Safai S, Weber DC, Lomax AJ 2017 Contour scanning for penumbra improvement in pencil beam scanned proton therapy. Phys Med Biol. 62 2398-2416.

Meijers A, Jakobi A, Stützer K, Guterres Marmitt G, Both S, Langendijk JA, Richter C, Knopf A. Log file-based dose reconstruction and accumulation for 4D adaptive pencil beam scanned proton therapy in a clinical treatment planning system: Implementation and proof-of-concept. Med Phys. 2019 Mar;46(3):1140-1149. doi: 10.1002/mp.13371.

Mercieca S, Pan S, Belderbos J, Salem A, Tenant S, Aznar MC, Woolf D, Radhakrishna G, van Herk M. 2020 Impact of Peer Review in Reducing Uncertainty in the Definition of the Lung Target Volume Among Trainee Oncologists. Clin Oncol (R Coll Radiol). Feb 4. pii: S0936-6555(20)30026-1. doi: 10.1016/j.clon.2020.01.026.

MEVION Website 2019, www.mevion.com

Mohan R, Grosshans D. Proton therapy - Present and future. Adv Drug Deliv Rev. 2017 Jan 15;109:26-44. doi: 10.1016/j.addr.2016.11.006. Review.

Mohan R, Das IJ, Ling CC. Empowering Intensity Modulated Proton Therapy Through Physics and Technology: An Overview. Int J Radiat Oncol Biol Phys. 2017 Oct 1;99(2):304-316. doi: 10.1016/j.ijrobp.2017.05.005. Review.

Monti, S., C. Paganelli, G. Buizza, L. Preda, F. Valvo, G. Baroni, G. Palma and L. Cella (2020). "A novel framework for spatial normalization of dose distributions in voxel-based analyses of brain irradiation outcomes." Phys Med 69: 164-169.

Morgan, M. A. and T. S. Lawrence. "Molecular Pathways: Overcoming Radiation Resistance by Targeting DNA Damage Response Pathways." Clin Cancer Res 2015 21(13): 2898-2904

Mori S, Knopf A C and Umegaki K 2018 Motion management in particle therapy Med Phys 45 e994-e1010

Müller BS, Wilkens JJ. 2016. Prioritized efficiency optimization for intensity modulated proton therapy. Phys Med Biol. 2016, Dec 7;61(23):8249-8265 https://doi.org/10.1088/0031-9155/61/23/8249.

Muller B S, Duma M N, Kampfer S, Nill S, Oelfke U, Geinitz H and Wilkens J J 2015 Impact of

interfractional changes in head and neck cancer patients on the delivered dose in intensity modulated radiotherapy with protons and photons Phys Med 31 266-72

Mutic S, Dempsey JF. 2014 The ViewRay system: magnetic resonance-guided and controlled radiotherapy. Semin Radiat Oncol. Jul;24(3):196-9.

Nagle PW, Hosper NA, Barazzuol L, Jellema AL, Baanstra M, van Goethem MJ, Brandenburg S, Giesen U, Langendijk JA, van Luijk P, Coppes RP5 2018 Lack of DNA Damage Response at Low Radiation Doses in Adult Stem Cells Contributes to Organ Dysfunction. Clin Cancer Res. 2018 24 6583-6593.

Nederveen AJ, Dehnad H, van der Heide UA, van Moorselaar RJ, Hofman P, Lagendijk JJ. 2003 Comparison of megavoltage position verification for prostate irradiation based on bony anatomy and implanted fiducials. Radiother Oncol. Jul;68(1):81-8

Nenoff, L., Matter, M., Hedlund Lindmar, J., Weber, D.C., Lomax, A.J., Albertini, F., Daily adaptive proton therapy - the key to innovative planning approaches for paranasal cancer treatments. Acta Oncol. 2019 Jul 31:1-6. doi: 10.1080/0284186X.2019.1641217

Nenoff L, Ribeiro CO, Matter M, Hafner L, Josipovic M, Langendijk JA, Persson GF, Walser M, Weber DC, Lomax AJ, Knopf AC, Albertini F, Zhang Y. 2020 Deformable image registration uncertainty for inter-fractional dose accumulation of lung cancer proton therapy. Radiother Oncol. 147 178-185.

Nesteruk KP, Calzolaio C, Meer D, Rizzoglio V, Seidel M, Schippers JM. 2019. Large energy acceptance gantry for proton therapy utilizing superconducting technology. Phys Med Biol. 2019, Jul 4. https://doi.org/10.1088/1361-6560/ab2f5f.

Nie K, Pouliot J, Smith E, Chuang C 2016 Performance variations among clinically available deformable image registration tools in adaptive radiotherapy - how should we evaluate and interpret the result? J Appl Clin Med Phys. 17 328-340.

Niemierko, A., J. Schuemann, M. Niyazi, D. Giantsoudi, G. Maquilan, H. Shih, and H. Paganetti (2020). " Brain necrosis in adult patients after proton therapy: Is there evidence for variable relative biological effectiveness?" Int J Radiat Oncol Biol Phys; under review.

Niepel K, Kamp F, Kurz C, Hansen D, Rit S, Neppl S, Hofmaier J, Bondesson D, Thieke C, Dinkel J, Belka C, Parodi K, Landry G. Feasibility of 4DCBCT-based proton dose calculation: An ex vivo porcine lung phantom study. Z Med Phys. 2018 Nov 14. pii: S0939-3889(18)30066-7. doi: 10.1016/j.zemedi.2018.10.005.

Nomura Y, Xu Q, Shirato H, Shimizu S and Xing L 2019 Projection-domain scatter correction for cone beam computed tomography using a residual convolutional neural network Med Phys 46 3142-55

Oborn B, Dowdell S, Metcalfe PE, Crozier S, Mohan R, Keall PJ. Proton beam deflection in MRI fields: implications for MRI-guided proton therapy. Med Phys. 2015;42:2113–2124.

Oborn BM , Dowdell S, Metcalfe PE, Crozier S, Mohan R, Keall PJ. 2017 Future of medical physics: Real-time MRI-guided proton therapy. Med Phys. Aug;44(8):e77-e90

Ogata R, Mori S, Yasuda S. Extended phase-correlated rescanning irradiation to improve dose homogeneity in carbon-ion beam liver treatment. Phys Med Biol. 2014 Sep 7;59(17):5091-9. doi: 10.1088/0031-9155/59/17/5091.

Paganetti H 2011 Proton therapy physics: CRC Press)

Paganetti H 2012 Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol. 57 R99-117

Paganetti, H. (2014). "Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer." Phys Med Biol 59(22): R419-472.

Paganetti, H. (2017). "Relating the proton relative biological effectiveness to tumor control and normal tissue complication probabilities assuming interpatient variability in alpha/beta." Acta Oncol 56(11): 1379-1386.

Paganetti, H., E. Blakely, A. Carabe-Fernandez, D. J. Carlson, I. J. Das, L. Dong, D. Grosshans, K. D. Held, R. Mohan, V. Moiseenko, A. Niemierko, R. D. Stewart and H. Willers (2019). "Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy." Med Phys 46(3): e53-e78.

Paganetti, H., A. Niemierko, M. Ancukiewicz, L. E. Gerweck, M. Goitein, J. S. Loeffler and H. D. Suit (2002). "Relative biological effectiveness (RBE) values for proton beam therapy." Int J Radiat Oncol Biol Phys 53(2): 407-421.

Palma, G., S. Monti and L. Cella (2020). "Voxel-based analysis in radiation oncology: A methodological cookbook." Phys Med 69: 192-204.

Palma, G., S. Monti, M. Conson, R. Pacelli and L. Cella (2019). "Normal tissue complication probability (NTCP) models for modern radiation therapy." Semin Oncol 46(3): 210-218.

Palma, G., S. Monti, T. Xu, E. Scifoni, P. Yang, S. M. Hahn, M. Durante, R. Mohan, Z. Liao and L. Cella (2019). "Spatial Dose Patterns Associated With Radiation Pneumonitis in a Randomized Trial Comparing Intensity-Modulated Photon Therapy With Passive Scattering Proton Therapy for Locally Advanced Non-Small Cell Lung Cancer." Int J Radiat Oncol Biol Phys 104(5): 1124-1132.

Parodi K, Paganetti H, Shih HA, Michaud S, Loeffler JS, DeLaney TF, Liebsch NJ, Munzenrider JE, Fischman AJ, Knopf A, Bortfeld T. 2007 Patient study of in vivo verification of beam delivery and range, using positron emission tomography and computed tomography imaging after proton therapy. Int J Radiat Oncol Biol Phys. Jul 1;68(3):920-34.

Parodi K, Polf J, In vivo range verification in particle therapy, Med Phys. 2018; 45:e1036-e1050

Parodi K, In Vivo Treatment Verification, in "Proton Therapy Physics, Second Edition", edited by H. Paganetti, CRC Press, 2018

Parodi K Latest Developments in In-Vivo Imaging for Proton Therapy Br. J. Radiol. 2020; 93 20190787

Patch S K, Santiago-Gonzalez D and Mustapha B 2019 Thermoacoustic range verification in the presence of acoustic heterogeneity and soundspeed errors - Robustness relative to ultrasound image of underlying anatomy Med Phys 46 318-27

Pedroni E, Bacher R, Blattmann H, et al. The 200-MeV proton therapy project at the Paul Scherrer Institute: conceptual design and practical realization. Med Phys. 1995; 22:37–53. [PubMed: 7715569]

Pedroni E, Bearpark R, Bohringer T, et al. The PSI Gantry 2: a second generation proton scanning gantry. Z Med Phys. 2004;14:25–34.

Peeler, C. R., D. Mirkovic, U. Titt, P. Blanchard, J. R. Gunther, A. Mahajan, R. Mohan and D. R. Grosshans (2016). "Clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma." Radiother Oncol 121(3): 395-401.

Pepin MD, Tryggestad E, Wan Chan Tseung HS, Johnson JE, Herman MG, Beltran C. A Monte-Carlo-based and GPU-accelerated 4D-dose calculator for a pencil beam scanning proton therapy system. Med

Phys. 2018 Nov;45(11):5293-5304. doi: 10.1002/mp.13182.

Perko Z, van der Voort S R, van de Water S, Hartman C M, Hoogeman M and Lathouwers D 2016 Fast and accurate sensitivity analysis of IMPT treatment plans using Polynomial Chaos Expansion Physics in medicine and biology 61 4646-64

Peucelle C, Naurave C, Patriarca A, Hierso E, Fournier-Bidoz N, Martinez-Rovira I, Prezado Y, Proton minibeam radiation therapy: Experimental dosimetry evaluation, Med Phys. 2015, 42(12):7108-13 [PubMed 4935868]

Pflugfelder D, Wilkens J J and Oelfke U 2008 Worst case optimization: a method to account for uncertainties in the optimization of intensity modulated proton therapy Physics in medicine and biology 53 1689-700

Pinto M, Kröniger K, Bauer J, Nilsson R, Traneus E, Parodi K 2020 A Filtering Approach for PET and PG Predictions in a Proton Treatment Planning System Phys Med Biol 65 (9) 095014

Plowman P N 1983 The effects of conventionally fractionated, extended portal radiotherapy on the human peripheral blood count Int J Radiat Oncol Biol Phys 9 829-39

Poludniowski G , Allinson NM, Evans PM. 2015 Proton radiography and tomography with application to proton therapy. Br J Radiol. Sep;88(1053):20150134

Printz Ringbæk T, Simeonov Y, Witt M, Engenhart-Cabillic R, Kraft G, Zink K, Weber U. 2017. Modulation power of porous materials and usage as ripple filter in particle therapy. Phys Med Biol. 2017, Apr 7;62(7):2892-2909. https://doi.org/10.1088/1361-6560/aa5c28.

Prusator M, Ahmad S, Chen Y. TOPAS Simulation of the Mevion S250 compact proton therapy unit. J Appl Clin Med Phys. 2017;18:88–95.

Psoroulas S, Bula C, Actis O, Weber DC, Meer D. 2018. A predictive algorithm for spot position corrections after fast energy switching in proton pencil beam scanning. Med Phys. 2018, Nov;45(11):4806-4815. https://doi.org/10.1002/mp.13217.

Qin A, Sun Y, Liang J, Yan D. 2015 Evaluation of online/offline image guidance/adaptation approaches for prostate cancer radiation therapy. Int J Radiat Oncol Biol Phys. Apr 1;91(5):1026-33

Qin N, Botas P, Giantsoudi D, Schuemann J, Tian Z, Jiang SB, Paganetti H, Jia X 2016 Recent developments and comprehensive evaluations of a GPU-based Monte Carlo package for proton therapy. Phys Med Biol. 61 7347-7362

Raaymakers BW, Raaijmakers AJ, Lagendijk JJ. 2008 Feasibility of MRI guided proton therapy: magnetic field dose effects. Phys Med Biol. Oct 21;53(20):5615-22

Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, Glitzner M, Kotte ANTJ, van Asselen B, de Boer JCJ, Bluemink JJ, Hackett SL, Moerland MA, Woodings SJ, Wolthaus JWH, van Zijp HM, Philippens MEP, Tijssen R, Kok JGM, de Groot-van Breugel EN, Kiekebosch I, Meijers LTC, Nomden CN, Sikkes GG, Doornaert PAH, Eppinga WSC, Kasperts N, Kerkmeijer LGW, Tersteeg JHA, Brown KJ, Pais B, Woodhead P, Lagendijk JJW 2017 First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. Phys Med Biol. Nov 14;62(23):L41-L50

Radojcic M and Crompton N E A 2001 Age dependence of T-lymphocyte apoptosis induced by high-energy proton exposure Radiation and Environmental Biophysics 40 131-5

Radovinsky A, Minervini J V, Miller C E et. al, IEEE transact. Appl. superconductivity, vol. 24, 3,

(2014) 4402505

Rancati, T., C. Fiorino, G. Fellin, V. Vavassori, E. Cagna, V. Casanova Borca, G. Girelli, L. Menegotti, A. F. Monti, F. Tortoreto, S. Delle Canne and R. Valdagni (2011). "Inclusion of clinical risk factors into NTCP modelling of late rectal toxicity after high dose radiotherapy for prostate cancer." Radiother Oncol 100(1): 124-130.

Reis Ferreira M, Andreyev J, Mohammed K, Truelove L, Gowan S M, Li J, Gulliford S L, Marchesi J and Dearnaley D P 2019 Microbiota and radiotherapy-induced gastrointestinal side-effects (MARS) study: a large pilot study of the microbiome in acute and late radiation enteropathy Clinical Cancer Research clincanres.0960.2019

Ribeiro CO, Knopf A, Langendijk JA, Weber DC, Lomax AJ, Zhang Y. Assessment of dosimetric errors induced by deformable image registration methods in 4D pencil beam scanned proton treatment planning for liver tumours. Radiother Oncol. 2018 Jul;128(1):174-181. doi: 10.1016/j.radonc.2018.03.001.

Ribeiro CO, Meijers A, Korevaar EW, Muijs CT, Both S, Langendijk JA, Knopf A. Comprehensive 4D robustness evaluation for pencil beam scanned proton plans. Radiother Oncol. 2019 Jul;136:185-189. doi: 10.1016/j.radonc.2019.03.037.

Rostek, C., E. L. Turner, M. Robbins, S. Rightnar, W. Xiao, A. Obenaus and T. A. Harkness (2008). "Involvement of homologous recombination repair after proton-induced DNA damage." Mutagenesis 23(2): 119-129.

Routman D M, Garant A, Lester S C, Day C N, Harmsen W S, Sanheuza C T, Yoon H H, Neben-Wittich M A, Martenson J A, Haddock M G, Hallemeier C L and Merrell K W 2019 A Comparison of Grade 4 Lymphopenia With Proton Versus Photon Radiation Therapy for Esophageal Cancer Adv Radiat Oncol 4 63-9

Rudra S, Hui C, Rao Y J, Samson P, Lin A J, Chang X, Tsien C, Fergus S, Mullen D, Yang D, Thotala D, Hallahan D, Campian J L and Huang J 2018 Effect of Radiation Treatment Volume Reduction on Lymphopenia in Patients Receiving Chemoradiotherapy for Glioblastoma Int J Radiat Oncol Biol Phys 101 217-25

Rutkowska, E., C. Baker and A. Nahum (2010). "Mechanistic simulation of normal-tissue damage in radiotherapy--implications for dose-volume analyses." Phys Med Biol 55(8): 2121-2136.

Sadrozinski H F, Geoghegan T, Harvey E, Johnson R P, Plautz T E, Zatserklyaniy A, Bashkirov V, Hurley R F, Piersimoni P, Schulte R W, Karbasi P, Schubert K E, Schultze B and Giacometti V 2016 Operation of the Preclinical Head Scanner for Proton CT Nucl Instrum Methods Phys Res A 831 394-9

Salama A K, Postow M A and Salama J K 2016 Irradiation and immunotherapy: From concept to the clinic Cancer 122 1659-71

Schellhammer SM, Hoffmann AL, Gantz S, Smeets J, van der Kraaij E, Quets S, Pieck S, Karsch L, Pawelke J. 2018 Integrating a low-field open MR scanner with a static proton research beam line: proof of concept. Phys Med Biol. Nov 22;63(23):23LT01

Schiavi A, Senzacqua M, Pioli S, Mairani A, Magro G, Molinelli S, Ciocca M, Battistoni G, Patera V 2017 Fred: a GPU-accelerated fast-Monte Carlo code for rapid treatment plan recalculation in ion beam therapy. Phys Med Biol. 62 7482-7504

Schillo M et al., Compact superconducting 250 MeV proton cyclotron for the PSI PROSCAN proton therapy project, F.Marti (ed), Cyclotrons and their applications 2001, p37-39 22

Schippers JM, Lomax AJ. 2011. Emerging technologies in proton therapy. Acta Oncol. 2011,

Aug;50(6):838-50. https://doi.org/10.3109/0284186X.2011.582513.

Scott J G, Berglund A, Schell M J, Mihaylov I, Fulp W J, Yue B, Welsh E, Caudell J J, Ahmed K, Strom T S, Mellon E, Venkat P, Johnstone P, Foekens J, Lee J, Moros E, Dalton W S, Eschrich S A, McLeod H, Harrison L B and Torres-Roca J F 2017 A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study The lancet oncology 18 202-11

Semenenko, V. A. and X. A. Li (2008). "Lyman-Kutcher-Burman NTCP model parameters for radiation pneumonitis and xerostomia based on combined analysis of published clinical data." Phys Med Biol 53(3): 737-755.

Seppenwoolde, Y., K. De Jaeger, L. J. Boersma, J. S. Belderbos and J. V. Lebesque (2004). "Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer." Int J Radiat Oncol Biol Phys 60(3): 748-758.

Sethi, R. V., D. Giantsoudi, M. Raiford, I. Malhi, A. Niemierko, O. Rapalino, P. Caruso, T. I. Yock, N. J. Tarbell, H. Paganetti and S. M. MacDonald (2014). "Patterns of failure after proton therapy in medulloblastoma; linear energy transfer distributions and relative biological effectiveness associations for relapses." Int J Radiat Oncol Biol Phys 88(3): 655-663.

Seyedin S N, Schoenhals J E, Lee D A, Cortez M A, Wang X, Niknam S, Tang C, Hong D S, Naing A, Sharma P, Allison J P, Chang J Y, Gomez D R, Heymach J V, Komaki R U, Cooper L J and Welsh J W 2015 Strategies for combining immunotherapy with radiation for anticancer therapy Immunotherapy 7 967-80

Shakirin G, Braess H, Fiedler F, Kunath D, Laube K, Parodi K, Priegnitz M, Enghardt W, Implementation and workflow for PET monitoring of therapeutic ion irradiation: a comparison of in-beam, in-room, and off-line techniques, Phys Med Biol. 2011; 56:1281-98

Sheehy S L: High intensity and other world wide developments in FFAG accelerators, Proceedings of Cyclotrons2016 2016, THD01 374-379

Shirato H, Onimaru R, Ishikawa M, Kaneko J, Takeshima T, Mochizuki K, Shimizu S, Umegaki K. Real-time 4-D radiotherapy for lung cancer. Cancer Sci. 2012 Jan;103(1):1-6. doi: 10.1111/j.1349-7006.2011.02114.x.

Stone, H. B., C. N. Coleman, M. S. Anscher and W. H. McBride (2003). "Effects of radiation on normal tissue: consequences and mechanisms." Lancet Oncol 4(9): 529-536.

Suit H D and Goitein M 1974 Dose-limiting tissues in relation to types and location of tumours: implications for efforts to improve radiation dose distributions Eur J Cancer 10 217-24

Suit H D, Goitein M, Tepper J, Koehler A M, Schmidt R A and Schneider R 1975 Exploratory study of proton radiation therapy using large field techniques and fractionated dose schedules Cancer 35 1646-57

Suit H D, Goitein M, Tepper J E, Verhey L, Koehler A M, Schneider R and Gragoudas E 1977 Clinical experience and expectation with protons and heavy ions Int J Radiat Oncol Biol Phys 3 115-25

Suzuki K, Palmer MB, Sahoo N, Zhang X, Poenisch F, Mackin DS, Liu AY, Wu R, Zhu XR, Frank SJ, Gillin MT, Lee AK. 2016. Quantitative analysis of treatment process time and throughput capacity for spot scanning proton therapy. Med Phys. 2016, Jul;43(7):3975. https://doi.org/10.1118/1.4952731.

Szeto YZ, Witte MG, van Kranen SR, Sonke J-J, Belderbos J, van Herk M. 2016 Effects of anatomical changes on pencil beam scanning proton plans in locally advanced NSCLC patients. Radiother Oncol 120 286–92

Taasti VT, Bäumer C, Dahlgren CV, Deisher AJ, Ellerbrock M, Free J, et al. Inter-centre variability of CT-based stopping-power prediction in particle therapy: Survey-based evaluation. Physics and Imaging in Radiation Oncology. 2018;6: 25–30.

Tang C, Liao Z, Gomez D, Levy L, Zhuang Y, Gebremichael R A, Hong D S, Komaki R and Welsh J W 2014 Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes Int J Radiat Oncol Biol Phys 89 1084-91

Tian L, Landry G, Dedes G, Kamp F, Pinto M, Niepel K, Belka C, Parodi, Toward a new treatment planning approach accounting for in vivo proton range verification, Phys Med Biol. 2018; 63:215025

Tian L, Landry G, Dedes G, Pinto M, Kamp F, Belka C, Parodi K 2020 A New Treatment Planning Approach Accounting for Prompt Gamma Range Verification and Interfractional Anatomical Changes, Phys Med Biol 65(9) 095005

Trbojevic D, Parker B, Keil E and Sessler A M: Carbon/proton therapy: A novel gantry design, Phys.Rev Special Topics, Acc,Beams, 10, 053503 (2007)

Trbojevic D, Alessi J, Blaskiewicz M et al., Lattice design of a rapid cycling medical synchrotron for carbon/proton therapy, Proceedings of IPAC2011, San Sebastián, Spain. 2011, http://www-linac.kek.jp/mirror/IPAC2011/papers/weps028.pdf.

Troeller, A., D. Yan, O. Marina, D. Schulze, M. Alber, K. Parodi, C. Belka and M. Sohn (2015). "Comparison and limitations of DVH-based NTCP models derived from 3D-CRT and IMRT data for prediction of gastrointestinal toxicities in prostate cancer patients by using propensity score matched pair analysis." Int J Radiat Oncol Biol Phys 91(2): 435-443.

Tsuboi K 2018 Advantages and Limitations in the Use of Combination Therapies with Charged Particle Radiation Therapy International Journal of Particle Therapy 122-32

Tucker, S. L., T. Xu, H. Paganetti, T. Deist, V. Verma, N. Choi, R. Mohan and Z. Liao (2019). "Validation of Effective Dose as a Better Predictor of Radiation Pneumonitis Risk Than Mean Lung Dose: Secondary Analysis of a Randomized Trial." Int J Radiat Oncol Biol Phys 103(2): 403-410.

Twyman-Saint Victor C, Rech A J, Maity A, Rengan R, Pauken K E, Stelekati E, Benci J L, Xu B, Dada H, Odorizzi P M, Herati R S, Mansfield K D, Patsch D, Amaravadi R K, Schuchter L M, Ishwaran H, Mick R, Pryma D A, Xu X, Feldman M D, Gangadhar T C, Hahn S M, Wherry E J, Vonderheide R H and Minn A J 2015 Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer Nature 520 373

Umezawa, Ebina F, Fujii Y et al., Hitachi Review Vol 64 (2015), No. 8.

Underwood, T. S. A., C. Grassberger, R. Bass, S. M. MacDonald, N. M. Meyersohn, B. Y. Yeap, R. B. Jimenez and H. Paganetti (2018). "Asymptomatic Late-phase Radiographic Changes Among Chest-Wall Patients Are Associated With a Proton RBE Exceeding 1.1." Int J Radiat Oncol Biol Phys 101(4): 809-819.

Unkel S, Belka C, Lauber K 2016 . On the analysis of clonogenic survival data: Statistical alternatives to the linear-quadratic model. Radiat Oncol. doi: 10.1186/s13014-016-0584-z.

Unkelbach J, Alber M, Bangert M, Bokrantz R, Chan T C, Deasy J O, Fredriksson A, Gorissen B L, Van Herk M and Liu W 2018 Robust radiotherapy planning Physics in Medicine & Biology 63 22TR02

Unkelbach J, Bortfeld T, Martin B C and Soukup M 2009 Reducing the sensitivity of IMPT treatment plans to setup errors and range uncertainties via probabilistic treatment planning Medical physics 36 149-63

Unkelbach, J., P. Botas, D. Giantsoudi, B. L. Gorissen and H. Paganetti (2016). "Reoptimization of Intensity Modulated Proton Therapy Plans Based on Linear Energy Transfer." Int J Radiat Oncol Biol Phys 96(5): 1097-1106.

Unkelbach J and Paganetti H 2018 Robust Proton Treatment Planning: Physical and Biological Optimization Semin Radiat Oncol 28 88-96

van de Water, S., Albertini, F., Weber, D.C., Heijmen, B.J.M., Hoogemann, M.S., Lomax, A.J., 2018 Anatomical robust optimization to account for nasal cavity filling variation during intensity-modulated proton therapy: a comparison with conventional and adaptive planning strategies, Phys. Med. Biol. 63 025020.

van de Water S, Kooy HM, Heijmen BJ, Hoogeman MS. 2015. Shortening delivery times of intensity modulated proton therapy by reducing proton energy layers during treatment plan optimization. Int J Radiat Oncol Biol Phys. 2015, Jun 1;92(2):460-8. https://doi.org/10.1016/j.ijrobp.2015.01.031.

van de Water S, Kraan A C, Breedveld S, Schillemans W, Teguh D N, Kooy H M, Madden T M, Heijmen B J M and Hoogeman M S 2013 Improved efficiency of multi-criteria IMPT treatment planning using iterative resampling of randomly placed pencil beams Phys. Med. Biol. 58 6969–83

van de Water, S., Safai, S., Schippers, J.M., Weber, D.C., Lomax, A.J. 2019, Towards FLASH proton therapy: the impact of treatment planning and machine characteristics on achievable dose rates. Acta Oncol. 26 1-7.

van Dijk LV, Van den Bosch L, Aljabar P, Peressutti D, Both S, J H M Steenbakkers R, Langendijk JA, Gooding MJ, Brouwer CL. Improving automatic delineation for head and neck organs at risk by Deep Learning Contouring. Radiother Oncol. 2019 Oct 22

van Elmpt W, Landry G, Das M, Verhaegen F. Dual Energy CT in Radiotherapy: Current Applications and Future Outlook. Radiother Oncol. 2016;119: 137–144.

van Luijk, P., H. Faber, J. M. Schippers, S. Brandenburg, J. A. Langendijk, H. Meertens and R. P. Coppes (2009). "Bath and shower effects in the rat parotid gland explain increased relative risk of parotid gland dysfunction after intensity-modulated radiotherapy." Int J Radiat Oncol Biol Phys 74(4): 1002-1005.

van Luijk, P., S. Pringle, J. O. Deasy, V. V. Moiseenko, H. Faber, A. Hovan, M. Baanstra, H. P. van der Laan, R. G. Kierkels, A. van der Schaaf, M. J. Witjes, J. M. Schippers, S. Brandenburg, J. A. Langendijk, J. Wu and R. P. Coppes (2015). "Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer." Sci Transl Med 7(305): 305ra147.

van Marlen P, Dahele M, Folkerts M, Abel E, Slotman BJ, Verbakel WFAR 2020 Bringing FLASH to the Clinic: Treatment Planning Considerations for Ultrahigh Dose-Rate Proton Beams. Int J Radiat Oncol Biol Phys.106 621-629.

van Ooteghem G, Dasnoy-Sumell D, Lambrecht M, Reychler G, Liistro G, Sterpin E, Geets X. Mechanically-assisted non-invasive ventilation: A step forward to modulate and to improve the reproducibility of breathing-related motion in radiation therapy. Radiother Oncol. 2019 Apr;133:132-139. doi: 10.1016/j.radonc.2018.12.026.

Vandevoorde C, Vral A, Vandekerckhove B, Philippe J and Thierens H 2016 Radiation Sensitivity of Human CD34(+) Cells Versus Peripheral Blood T Lymphocytes of Newborns and Adults: DNA Repair and Mutagenic Effects Radiat Res 185 580-90

Vatner R E, Cooper B T, Vanpouille-Box C, Demaria S and Formenti S C 2014 Combinations of immunotherapy and radiation in cancer therapy Frontiers in oncology 4 325

Vaupel P 2004 Tumor microenvironmental physiology and its implications for radiation oncology Seminars in radiation oncology 14 198-206

Veiga C, Janssens G, Teng C L, Baudier T, Hotoiu L, McClelland J R, Royle G, Lin L, Yin L, Metz J, Solberg T D, Tochner Z, Simone C B, 2nd, McDonough J and Teo B K First Clinical Investigation of Cone Beam Computed Tomography and Deformable Registration for Adaptive Proton Therapy for Lung Cancer Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):549-59. doi: 10.1016/j.ijrobp.2016.01.055.

Verbakel WFAR, Doornaert PAH, Raaijmakers CPJ, Bos LJ, Essers M, van de Kamer JB, Dahele M, Terhaard CHJ, Kaanders JHAM. Targeted Intervention to Improve the Quality of Head and Neck Radiation Therapy Treatment Planning in the Netherlands: Short and Long-Term Impact. Int J Radiat Oncol Biol Phys. 2019 Nov 1;105(3):514-524.

Verellen D, De Ridder M, Linthout N, Tournel K, Soete G, Storme G. 2007 Innovations in image-guided radiotherapy. Nat Rev Cancer. Dec;7(12):949-60

Vinod SK, Jameson MG, Min M, Holloway LC. Uncertainties in Volume Delineation in Radiation Oncology: A Systematic Review and Recommendations for Future Studies. Radiother Oncol. 2016a; 121: 169–179.

Vinod S K, Min M, Jameson M G and Holloway L C A Review of Interventions to Reduce Inter-Observer Variability in Volume Delineation in Radiation Oncology J. Med. Imaging Radiat. Oncol. 2016b; 60 393–406

Vretenar M, Dallocchio A, Dimov V A et al., A Compact High-Frequency RFQ For Medical Applications, , Proc. Of LINAC14, 2014, THPP040, p. 935-938.

Wang F, Flanz J, and Hamm R W: Injection Study of the ProTom-Radiance 330 Synchrotron with a 1.6 MeV RFQ Linac , The 19th Part.Nucl. Conference, 2011 Cambridge, MA, USA.

Wang Y, Deng W, Li N, Sharma A, Jiang W and Lin S H 2018 Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions Frotiers in Pharmacology 9 185

Wang Y, Mazur T R, Park J C, Yang D, Mutic S and Li H H 2017 Development of a fast Monte Carlo dose calculation system for online adaptive radiation therapy quality assurance Phys Med Biol 62 4970-90

Wang, C. C., A. L. McNamara, J. Shin, J. Schuemann, C. Grassberger, A. G. Taghian, R. B. Jimenez, S. M. MacDonald and H. Paganetti (2020). "End-of-Range Radiobiological Effect on Rib Fractures in Patients Receiving Proton Therapy for Breast Cancer." Int J Radiat Oncol Biol Phys 107(3): 449-454.

Widder J, van der Schaaf A, Lambin P, Marijnen CA, Pignol JP, Rasch CR, Slotman BJ, Verheij M, Langendijk JA. The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):30-6.

Widesott L, Pierelli A, Fiorino C, Lomax AJ, Amichetti M, Cozzarini C, Soukup M, Schneider R, Hug E, Di Muzio N, Calandrino R, Schwarz M 2011 Helical tomotherapy vs. intensity-modulated proton therapy for whole pelvis irradiation in high-risk prostate cancer patients: dosimetric, normal tissue complication probability, and generalized equivalent uniform dose analysis. Int J Radiat Oncol Biol Phys. 80 1589-600

Wild A T, Herman J M, Dholakia A S, Moningi S, Lu Y, Rosati L M, Hacker-Prietz A, Assadi R K, Saeed A M, Pawlik T M, Jaffee E M, Laheru D A, Tran P T, Weiss M J, Wolfgang C L, Ford E, Grossman S A, Ye X and Ellsworth S G 2016 Lymphocyte-Sparing Effect of Stereotactic Body Radiation Therapy

in Patients With Unresectable Pancreatic Cancer. International Jornal of Radiation Oncology, Biology, Physics 94 571-9

Wilkens JJ, Alaly JR, Zakarian K, Thorstad WL, Deasy JO. IMRT treatment planning based on prioritizing prescription goals. Phys Med Biol. 2007 Mar 21;52(6):1675-92.

Wilkens J J and Oelfke U 2005 Optimization of radiobiological effects in intensity modulated proton therapy Medical physics 32 455-65

Willemink MJ, Persson M, Pourmorteza A, Pelc NJ, Fleischmann D. Photon-Counting CT: Technical Principles and Clinical Prospects. Radiology. 2018;289: 293–312.

Willers, H., A. Allen, D. Grosshans, S. J. McMahon, C. von Neubeck, C. Wiese and B. Vikram (2018). "Toward A variable RBE for proton beam therapy." Radiother Oncol 128(1): 68-75.

Wilson R R 1946 Radiological Use of Fast Protons Radiology 47 487-91

Winterhalter C, Fura E, Tian Y, Aitkenhead A, Bolsi A, Dieterle M, Fredh A, Meier G, Oxley D, Siewert D, Weber DC, Lomax A, Safai S. Validating a Monte Carlo approach to absolute dose quality assurance for proton pencil beam scanning. Phys Med Biol. 2018 Aug 23;63(17):175001. doi: 10.1088/1361-6560/aad3ae.

Wohlfahrt P, Richter C. Status and innovations in pre-treatment CT imaging for proton therapy. The British Journal of Radiology. 2020;92: 20190590.

Wong Yuzhen N, Barrett S. A review of automatic lung tumour segmentation in the era of 4DCT. Rep Pract Oncol Radiother. 2019 Mar-Apr;24(2):208-220. doi: 10.1016/j.rpor.2019.01.003.

Wopken K, Bijl HP, van der Schaaf A, van der Laan HP, Chouvalova O, Steenbakkers RJ, Doornaert P, Slotman BJ, Oosting SF, Christianen ME, van der Laan BF, Roodenburg JL, Leemans CR, Verdonck-de Leeuw IM, Langendijk JA 2014 Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after curative radiotherapy/chemo-radiotherapy in head and neck cancer. Radiother Oncol. 113 95-101.

Xiang M, Chang DT, Pollom EL. Second cancer risk after primary cancer treatment with three-dimensional conformal, intensity-modulated, or proton beam radiation therapy. Cancer. 2020;126(15):3560-8.

Xie Y, Bentefour E H, Janssens G, Smeets J, Vander Stappen F, Hotoiu L, Yin L, Dolney D, Avery S, O'Grady F, Prieels D, McDonough J, Solberg T D, Lustig R A, Lin A and Teo B K 2017 Prompt Gamma Imaging for In Vivo Range Verification of Pencil Beam Scanning Proton Therapy Int J Radiat Oncol Biol Phys 99 210-8

Yan D, Vicini F, Wong J, Martinez A. 1997 Adaptive radiation therapy Phys Med Biol. Jan;42(1):123-32.

Yan D, Wong J, Vicini F, Michalski J, Pan C, Frazier A, Horwitz E, Martinez A 1997. Adaptive modification of treatment planning to minimize the deleterious effects of treatment setup errors. Int J Radiat Oncol Biol Phys. 38 197-206.

Yan S, Lu HM, Flanz J., Adams J., Trofimov A, Bortfeld T., Reassessment of the Necessity of the Proton Gantry: Analysis of Beam Orientations from 4332 Treatments at the Massachusetts General Hospital Proton Center Over the Past 10 Years., Int J Radiat Oncol Biol Phys 2016, 95(1): 224-33.

Yang M, Zhu X R, Park P C, Titt U, Mohan R, Virshup G, Clayton J E and Dong L 2012 Comprehensive analysis of proton range uncertainties related to patient stopping-power-ratio estimation using the

stoichiometric calibration Phys Med Biol 57 4095-115

Yang P, Xu T, Gomez D R, Deng W, Wei X, Elhalawani H, Jin H, Guan F, Mirkovic D, Xu Y, Mohan R and Liao Z 2019 Patterns of Local-Regional Failure After Intensity Modulated Radiation Therapy or Passive Scattering Proton Therapy With Concurrent Chemotherapy for Non-Small Cell Lung Cancer Int J Radiat Oncol Biol Phys 103 123-31

Yang Z, Zhang X, Wang X, Zhu XR, Gunn B, Frank SJ, Chang Y, Li Q, Yang K, Wu G, Liao L, Li Y, Chen M, Li H. 2020 Multiple-CT optimization: An adaptive optimization method to account for anatomical changes in intensity-modulated proton therapy for head and neck cancers. Radiother Oncol. 142 124-132

Yard B D, Adams D J, Chie E K, Tamayo P, Battaglia J S, Gopal P, Rogacki K, Pearson B E, Phillips J, Raymond D P, Pennell N A, Almeida F, Cheah J H, Clemons P A, Shamji A, Peacock C D, Schreiber S L, Hammerman P S and Abazeed M E 2016 A genetic basis for the variation in the vulnerability of cancer to DNA damage Nature Communications 7 11428

Yorke, E. D. (2001). "Modeling the effects of inhomogeneous dose distributions in normal tissues." Semin Radiat Oncol 11(3): 197-209.

Yoshida E, Tashima H, Nagatsu K, Tsuji AB, Kamada K, Parodi K, Yamaya T 2020 Whole Gamma Imaging: A New Concept of PET Combined With Compton Imaging, Phys Med Biol 65 125013

Younkin J., Bues M., et. al., Multiple energy extraction reduces beam delivery time for a synchrotron-based proton spot-scanning system, Adv Radiat Oncol. 2018, Feb 23;3(3):412-420. https://doi.org/10.1016/j.adro.2018.02.006.

Yovino S, Kleinberg L, Grossman S A, Narayanan M and Ford E 2013 The etiology of treatment-related lymphopenia in patients with malignant gliomas: modeling radiation dose to circulating lymphocytes explains clinical observations and suggests methods of modifying the impact of radiation on immune cells Cancer Invest 31 140-4

Zeil K, Baumann M, Beyreuther E, Burris-Mog T, Cowan T E et al.: “Dose-controlled irradiation of cancer cells with laser-accelerated proton pulses” Appl. Phys. B 110: 437-444, 2013

Zhang M, Westerly D C and Mackie T R. Introducing an on-line adaptive procedure for prostate image guided intensity modulate proton therapy. Phys. Med. Biol. 56 (2011) 4947–4965 doi:10.1088/0031-9155/56/15/019

Zhang Y, Knopf A, Tanner C, Lomax AJ. Online image guided tumour tracking with scanned proton beams: a comprehensive simulation study. Phys Med Biol. 2014 Dec 21;59(24):7793-817. doi: 10.1088/0031-9155/59/24/7793.

Zhu XR, Li Y, Mackin D, Li H, Poenisch F, Lee AK, Mahajan A, Frank SJ, Gillin MT, Sahoo N, Zhang X. Towards effective and efficient patient-specific quality assurance for spot scanning proton therapy. Cancers (Basel). 2015 Apr 10;7(2):631-47. doi: 10.3390/cancers7020631.